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RATE OF REGENERATION IN HUMAN PERIPHERAL NERVES

Analysis of the Interval Between Injury and Onset of Recovery

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THOUGH valuable information continues to accumulate regarding the reparative process following experimental nerve injuries in lower mammals, the available information relating to repair in human material remains incomplete and is still too meager to enable one to determine whether the experimental results are directly applicable to man.

In the present inquiry an attempt has been made to calculate the rate of regeneration after lesions of human peripheral nerves and to analyze the events that occur in the interval between the injury and the onset of clinical recovery. The importance of this information in regard to the treatment and prognosis of peripheral nerve injuries is self evident. The investigation was commenced at an Australian military hospital in 1940, when it was apparent that large numbers of patients with nerve injuries would again come under observation. All the patients here reported on remained under my care until either (a) recovery was complete or sufficiently advanced to warrant the patient's return to service or (b) the anticipated period of incapacity rendered such a return unlikely. In the latter event the patient was discharged from the service and transferred to the Department of Repatriation, where the facilities provided have enabled observations to be continued over a period of six years. The examinations throughout were conducted by the same observer, considerably reducing the personal factor introduced by the transferring of patients from clinic to clinic. Investigations relating to the rate of regeneration in individual peripheral nerves and of motor and sensory fibers have already been reported.¹ A general review and a discussion of the problems relating to this aspect of repair are now possible.

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1. Sunderland, S.: (a) Course and Rate of Regeneration of Motor Fibers Following Lesions of the Radial Nerve, *Arch. Neurol. & Psychiat.* **56**:133-157 (Aug.) 1946; (b) Rate of Regeneration of Motor Fibers in the Ulnar and Sciatic Nerves, *ibid.* **58**:7-13 (July) 1947; (c) Rate of Regeneration of Sensory Nerve Fibers, *ibid.* **58**:1-6 (July) 1947.

TERMINOLOGY AND TREATMENT

Latent Period.—The interval between the injury and the onset of clinical recovery is termed the latent period.

Initial Delay.—The interval between the injury and the time when functionally mature fibers appear in the distal segment is termed the initial, or scar, delay, though others² have defined it as the latent period.

Period of Growth and Maturation.—This is the time taken (a) by regenerating axons to descend along the distal segment and to reach muscle or skin and (b) for the changes to take place which convert the axon into a functionally mature nerve fiber.

Terminal Delay.—This is the time required for the intramuscular and intradermal changes which permit a motor response to voluntary effort and the correct interpretation of a peripheral stimulus. This implies the reestablishment of functional end organ relationships in sufficient numbers and in the appropriate patterns for functional recovery.

Infection and Scarring.—In order to evaluate the influence of these factors on the course of regeneration, an attempt was made in each case to assess the degree of infection and local scarring about the nerve. This was difficult, and only the simplest classification into "significant" and "insignificant" was attempted. The degree of infection was assessed on the basis of general symptoms, culture of material from the wound, the presence or absence of osteomyelitis, the period during which the wound discharged, the time taken for the wound to heal and the extent of the residual scarring. The degree of scarring was estimated on the extent of the injury to soft tissue, the area and density of the residual scar and whether this was adherent, free, depressed or otherwise.

Motor Recovery.—The criteria adopted for ascertaining the return of function were: (a) palpable contraction of a muscle or (b) movement which was undoubtedly attributable to action of the muscle alone. Due regard was paid to the possibility of transmitted contraction and trick movements. In order to detect the earliest signs of recovery, patients were examined at weekly intervals until all muscles were contracting; from then on the examinations were conducted at monthly intervals, then every three months and finally every six months. When weekly examinations were not possible, and the first appearance of recovery could therefore not be attributed to a specific week, two dates were supplied: (a) the last date when the muscle was known to be still paralyzed and (b) the date when recovery was first detected.

2. (a) Gutmann, E.; Gutmann, L.; Medawar, P. B., and Young, J. Z.: The Rate of Regeneration of Nerve, *J. Exper. Biol.* **19**:14-44 (May) 1942. (b) Seddon, H. J.; Medawar, P. B., and Smith, H.: Rate of Regeneration of Peripheral Nerves in Man, *J. Physiol.* **102**:191-215 (Sept. 30) 1943.

Treatment.—Treatment in all cases consisted of daily massage, heat therapy, exercises and supervised and controlled splinting. Electrotherapy was not employed. All muscles were splinted in a position of rest (just sufficient to remove tension) until contraction appeared. These points are mentioned because evidence has been obtained from this study that rest of paralyzed muscles hastens recovery and stretch delays it, while there is evidence to suggest that electrotherapy accelerates the recovery of muscle weight and strength without, apparently, affecting the time of onset of recovery.³ Therefore, since therapy appears to have a certain effect on the onset and progress of recovery, the treatment should be described in any study of rates of regeneration.

PRELIMINARY ANATOMIC INVESTIGATION

For a detailed study of the regeneration which follows injury to any peripheral nerve, a precise knowledge of its anatomy is essential. For this reason, information was obtained on the following points through a dissection of 20 specimens each of the radial, median, ulnar and sciatic nerves: (1) the order and site of origin of individual motor branches measured from selected points on the nerve; (2) the average shortest and longest distances to individual muscles, together with the range of variation of these distances, measured from a selected point directly along the nerve and its branches. The distal point was that at which the nerve entered the muscle; this is mentioned because branches may, after joining a muscle, continue along its surface for some distance before entering it.

The nerves and their branches were dissected throughout their entire course. The measurements, to the nearest millimeter, were then made, *in situ*, directly along the nerve and its primary and succeeding branches. The presence of multiple branches to muscles made it necessary to study all distances to individual muscles; the shortest and longest distances were obtained regardless of the order in which the branches left the nerve. For the detailed results of this preliminary anatomic investigation, the reader is referred to a series of papers deal-

3. Fischer, E.: The Effect of Faradic and Galvanic Stimulation upon the Course of Atrophy in Denervated Skeletal Muscles, *Am. J. Physiol.* **127**:605-619 (Nov.) 1939. Hines, H. M.: Effects of Immobilization and Activity on Neuromuscular Regeneration, *J. A. M. A.* **120**:515-517 (Oct. 17) 1942. Gutmann, E., and Gutmann, L.: Effect of Electrotherapy on Denervated Muscles in Rabbits, *Lancet* **1**:169-170 (Feb. 7) 1942. Hines, H. M., and Lazere, B.: Physiologic Basis for Treatment of Paralyzed Muscle, *Arch. Phys. Therapy* **24**:69-73 (Feb.) 1943. Gutmann, E., and Gutmann, L.: The Effect of Galvanic Exercise on Denervated and Re-Innervated Muscles in the Rabbit, *J. Neurol., Neurosurg. & Psychiat.* **7**:7-17 (Jan.-April) 1944. Jackson, E. C. S., and Seddon, H. J.: Influence of Galvanic Stimulation on Muscle Atrophy Resulting from Denervation, *Brit. M. J.* **2**:485-486 (Oct. 13) 1945. Jackson, S.: The Role of Galvanism in the Treatment of Denervated Voluntary Muscle in Man, *Brain* **68**:300-330 (Dec.) 1945.

ing with the metrical and nonmetrical features of the motor branches of human peripheral nerves.⁴ The average shortest distances from certain points to individual muscles, together with their standard deviations, are given in table 1. From the data, the distance from the site of a nerve lesion to the muscles can be estimated, provided that the distance of the lesion from the same points is known.

Linell⁵ measured, from fixed points, the level at which branches proceeded from the nerves of the arm and entered their respective muscles (his investigation was incomplete in that the nerve supply to some muscles was not studied). He pointed out, however, that his values referred only to horizontal levels, so that a measurement would not represent the actual length of a branch if it did not pass vertically down the limb. Since most branches do not pursue such a vertical course, his figures cannot be accepted as more than approximations of the length of these nerves. Again, Linell appears to have disregarded the fact that muscles may be supplied by multiple branches and that the branches to individual muscles may arise at widely spaced intervals. This is of importance in that the first branch to a muscle does not necessarily contain the shortest fibers to it.

Seddon, Medawar and Smith^{2b} used Linell's figures in a study of the rates of regeneration in human peripheral nerves. They also employed a hitherto unpublished series of measurements by Feinstein and Hight, of which details have not been provided, though it appears that Linell's methods were closely followed. In the two sets of figures included in their paper, a single value was given for the distance to each muscle. No reference was made to the range of variations in the distance to any one muscle, which is a factor of considerable importance in calculating rates of regeneration and in appreciating certain departures from what is regarded as the normal serial order of innervation.

Thus, in the case of the ulnar nerve, the length of the section between the hypothenar group of muscles and the first dorsal interosseous muscle was calculated by measuring the distances to each muscle from the same point on the nerve trunk and then subtracting the shorter from the longer distance. Feinstein and Hight gave a value of 30 mm. for this

4. Sunderland, S.: The Metrical and Non-Metrical Features of the Muscular Branches of the Radial Nerve, *J. Comp. Neurol.* **85**:93-111 (Aug.) 1946. Sunderland, S., and Hughes, E. S. R.: The Metrical and Non-Metrical Features of the Muscular Branches of the Ulnar Nerve, *ibid.* **85**:113-125 (Aug.) 1946. Sunderland, S., and Ray, L. J.: The Metrical and Non-Metrical Features of the Muscular Branches of the Median Nerve, *ibid.* **85**:191-203 (Oct.) 1946. Sunderland, S., and Hughes, E. S. R.: The Metrical and Non-Metrical Features of the Muscular Branches of the Sciatic Nerve and Its Medial and Lateral Popliteal Divisions, *ibid.* **85**:205-222 (Oct.) 1946.

5. Linell, E. A.: The Distribution of Nerves in the Upper Limb, with Reference to Variabilities and Their Clinical Significance, *J. Anat.* **55**:79-112, 1921.

TABLE 1.—*Shortest Distances to Muscles (in Millimeters)*

Muscle	Taken (1) 10 Cm. Above L. H. E. (Radial) and M. H. E. (Ulnar and Median Nerves); (2) 5 Cm. Above I. T. T. (Thigh Muscles); (3) 5 Cm. Above M. F. E. (Calf Muscles and Popliteus), and (4) at M. F. E. (Rest)*		Taken from Level of Styloid Process of Radius	
	Mean	Standard Deviation	Mean	Standard Deviation
Radial nerve †				
B. R.	82	15
E. C. R. L.	105	11
E. C. R. B.	147	19
E. D. C.	202	21
E. C. U.	202	20
E. D. Q.	217	25
A. P. L.	214	21
E. P. L.	239	23
E. P. B.	259	30
E. I. P.	269	30
Ulnar nerve ‡				
F. C. U.	133	10
F. D. P.	160	13
A. M. D.	33	13
F. M. D.	42	12
O. M. D.	44	12
Hypothenar §....	32	11
I. 4	56	11
I. 3	61	13
I. 2	71	10
I. 1	82	9
L. 4	75	10
L. 3	75	12
A. O.	75	10
A. T.	77	11
Median nerve 				
P. T.	129	12
F. C. R.	159	12
F. D. S.	154	12
F. D. P.	193	21
F. P. L.	200	32
P. Q.	298	34
Thenar	55	13
L. 1	69	12
L. 2	74	12
Sciatic nerve ¶				
L. B.	161	40
S. B.	271	35
S. T.	124	23
S. M.	246	30
A. M.	212	34
M. G.	82	11
L. G.	56	18
G. §	81	12
S.	131	20
P.	131	16
T. P.	106	26
F. D. L.	174	30
F. H. L.	215	36
P. L.	94	23
P. B.	196	32
T. A.	103	11
E. D. L.	102	20
E. H. L.	181	29
Pt.	257	26

* L. H. E. and M. H. E. indicate, respectively, the lateral and medial humeral epicondyle; M. F. E. indicates the medial femoral epicondyle and I. T., the ischial tuberosity.

† For the radial nerve, B. R. denotes brachioradialis; E. C. R. L., extensor carpi radialis longus; E. C. R. B., extensor carpi radialis brevis; E. D. C., extensor digitorum communis; E. C. U., extensor carpi ulnaris; E. D. Q., extensor digiti quinti proprius; A. P. L., abductor pollicis longus; E. P. L., extensor pollicis longus; E. P. B., extensor pollicis brevis; E. I. P., extensor indicis proprius.

‡ For the ulnar nerve, F. C. U. denotes flexor carpi ulnaris; F. D. P., flexor digitorum profundus; A. M. D., abductor minimi digiti; F. M. D., flexor minimi digiti; O. M. D., opponens minimi digiti; I., interosseous (1-4); L., lumbricals; A. O., adductor pollicis, oblique head; A. T., adductor pollicis, transverse head.

§ Shortest distance to the hypothenar group and to the gastrocnemius muscle, regardless of the particular portion of the muscle supplied.

|| For the median nerve, P. T. denotes pronator teres; F. C. R., flexor carpi radialis; F. D. S., flexor digitorum sublimis; F. D. P., flexor digitorum profundus; F. P. L., flexor pollicis longus; P. Q., pronator quadratus; L., lumbricals.

¶ For the sciatic nerve, L. B. denotes long head of biceps; S. B., short head of biceps; S. T., semitendinosus; S. M., semimembranosus; A. M., adductor magnus; M. G., medial head of gastrocnemius; L. G., lateral head of gastrocnemius; G., gastrocnemius; S., soleus; P., plantaris; T. P., tibialis posterior; F. D. L., flexor digitorum longus; F. H. L., flexor hallucis longus; P. L., peroneus longus; P. B., peroneus brevis; T. A., tibialis anterior; E. D. L., extensor digitorum longus; E. H. L., extensor hallucis longus; Pt., peroneus tertius.

length; the value reported by me was 49 ± 12 mm., and my observations show that their figure is too low for all but the exceptional person. The measurements of Linell and of Feinstein and Highet give the impression, too, that the serial order of innervation of muscles is a constant one, whereas, on the contrary, it is subject to considerable variation. It does not seem to have been appreciated that these variations are an important cause of departures from what is regarded as the normal rate and order of recovery. For example, Stopford⁶ recorded in some cases of lesions of the radial nerve that the extensor carpi ulnaris recovered before the extensor digitorum communis. Seddon, Medawar and Smith, having failed to confirm Stopford's observation, erroneously concluded, owing to the unreliable anatomic data at their disposal, that the earlier recovery of the extensor carpi ulnaris could not be expected on anatomic grounds. I have confirmed Stopford's observation, however, on several occasions, and it was supported by my anatomic investigation. Thus, in 7 specimens the distance to the extensor carpi ulnaris was less than that to the extensor digitorum communis, though in 2 specimens the difference was insignificant; in 11 specimens the distance to the extensor digitorum communis was less, but only significantly so in 4 specimens. In the remaining 2 specimens the figures for the two muscles were the same.

CLINICAL MATERIAL

Clinical observations, which form the basis of the discussion to follow, were made on a series of 301 patients, presenting 339 peripheral nerve injuries, who have been under continuous observation for periods ranging from one to six years. Case histories containing details of the injury and progress of recovery will be reported separately. The data relevant to the present inquiry are contained in tables 2, 3, 4 and 5, in which details are given relating to the following factors: (a) cause of the nerve injury and its level; (b) presence or absence of significant scarring and infection at the site of injury; (c) onset of recovery in muscles supplied by the radial, ulnar and sciatic nerves, and (d) advance of Tinel's sign. Additional data will be introduced in the appropriate sections of the text.

REVIEW OF METHODS PREVIOUSLY EMPLOYED TO CALCULATE THE RATE OF REGENERATION

Methods employed for calculating the rate of regeneration have one feature in common—they all measure the rate for a number of fibers in the nerve trunk, and not the rate for a single fiber.

6. Stopford, J. S. B.: The Results of Secondary Suture of Peripheral Nerves, *Brain* 43:1-25 (May 20) 1920.

TABLE 2.—Data Relating to the Lesions of the Radial Nerve

Causative Injury; Nature of Nerve Lesion; Case No.	Level of Lesion Above L. H. E., Cm.	Interval Between Injury and Suture, Days	Wound Infection	Scarring	Return of Voluntary Contraction, Weeks *						
					BR.	E. C. R. L.	E. D. C.	E. C. U.	A. P. L.	E. P. L.	
Axonotmesis											
Simple fracture of humerus.											
Case 77.....	10.0	..	Nil	Nil	16	18	23	23	25	27	
161.....	10.0	..	Nil	Nil	13	14	21	23	25	26	
317.....	10.0	..	Nil	Nil	16	18	24	22	25	29	
Gunshot wound											
Case 186.....	12.0	..	Nil	Nil	14	16	22	24	26	30	
203.....	9.0	..	Nil	Nil	20	20	27	27	31	31	
255.....	2.0	..	1†	8†	8	8	18	18	20	26	
294.....	1.0	..	Nil	8	Intact	14	23	23	25	34	
Gunshot wound + fracture of humerus											
Case 100.....	7.5	..	1	8	Intact	23	28-31	28-31	32-36	32-36	
106.....	5.0	..	1	8	17	20	27	30	31	36	
118.....	9.0	..	1	8	16	17-20	17-20	28	28	28	
231.....	12.5	..	1	8	40	42	45	50	56	56	
258.....	5.0	..	1	8	18	22	32	31	35	37	
Suture											
Laceration											
Case 180.....	4.0	38	Nil	S	28	20	31	31	34	42	
282.....	12.5	Immediate	Nil	Nil	22	27	37	36	40	45	
Gunshot wound											
Case 40.....	5.0	313	I	S	Intact	20	34	35	40	40	

* BR. Indicates brachioradialis; E. C. R. L., extensor carpi radialis longus; E. D. C., extensor digitorum communis; E. O. U., extensor carpi ulnaris;
A. P. L., abductor pollicis longus; E. P. L., extensor pollicis longus; L. H. E., lateral epicondyle of the humerus.
† I and S denote significant infection and scarring, respectively.

TABLE 3.—Data Relating to the Lesions of the Ulnar Nerve

Causative Injury; Nature of Nerve Lesion; Case No.	Level of Injury, Cm.*	M. H. E. to R. S. I.,*	Interval Between Injury and Suture, Days	Wound Infection	Return of Voluntary Contraction, Weeks †		
					Scarring	F. C. U.	H.
Axonotmesis	D. I.						
<i>Laceration</i>							
Case 103.....	5.0 above R. S. L. 2.0 below R. S. L.	Nil	S ‡	..	20 8
Case 323.....	Nil	Nil	..	32 20
Gunshot wound.....	Nil	Nil	..	79
Case 30.....	20.0 above R. S. L. 10.0 above M. H. E. 6.0 above M. H. E. 17.0 above M. H. E. 8.0 above M. H. E. 8.0 above R. S. L. 28.0 26.0 29.0 27.0	Nil Nil Nil Nil Nil	Nil Nil Nil Nil Nil	.. 27 4.33 15 1.20	62 80 90 20 22
Case 31.....	129.....	Nil	Nil	..	91
Case 136.....	179.....	Nil	Nil	..	107
Case 237.....	Nil	Nil	..	41
Gunshot wound + bone injury.....	Nil	Nil	..	30
Case 43.....	13.0 above R. S. L. 14.0 above R. S. L. 1.0 above R. S. L.	Nil	S	..	34
Case 176.....	176.....	Nil	Nil	..	42
Case 235.....	Nil	Nil	..	42
<i>Suture</i>							
<i>Compound fracture of radius and ulna</i>							
Case 328.....	15.0 above R. S. L.	29.5	177	Nil	Nil	..	32
<i>Laceration</i>							
Case 106.....	25.0 above R. S. L. 1.0 above R. S. L. 2.5 above M. H. E. 26.5 above R. S. L. At M. H. E. 8.0 above R. S. L.	30.0 27.5 29.0 25.0	2 Immediate 104 277 1 5	Nil Nil Nil Nil Nil Nil	Nil S S Nil Nil S 18 46 17 40	42 65 61 109 62 102
Case 139.....	158.....	Nil	Nil	..	47
Case 290.....	290.....	Nil	Nil	..	47
Case 325.....	325.....	Nil	Nil	..	47
Gunshot wound	Case 38.....	8.0 above R. S. L. 7.0 above M. H. E. 26.0	191 272	Nil Nil	Entirely by median sl
Case 183.....	183.....	Nil	Nil	..	63
Case 207.....	207.....	6.0 above M. H. E. 14.0 above M. H. E.	26.0 25.0	131 314	Nil 1	14 26	67 61
Case 277.....	277.....	Nil	Nil	..	Partly by median
Gunshot wound + bone injury	Case 100.....	6.0 above M. H. E. 9.0 above M. H. E. 16.0 above M. H. E.	26.5 26.5 29.0	320 Immediate 1,012	1 1	30 4.30 27	67 37 68
Case 243.....	243.....	93:125 55
Case 246.....	246.....	No recovery at 100 weeks

* R. S. L. and M. H. E. indicate levels of styloid process of the radius and medial epicondyle of the humerus, respectively.

† F. C. U. indicates flexor carpi ulnaris; H. indicates hypotenar muscles.

‡ I and S indicate significant infection and scarring, respectively.

EXPERIMENTAL METHODS

Gutmann, Gutmann, Medawar and Young.^{2a}—Five methods were employed by these investigators to measure the rate of advance of axon tips and to follow the process of maturation in the sciatic nerve of the rabbit (*a*) after cutting and suture and (*b*) after crushing. These will be discussed in the order in which they were described. It is to be noted that these authors used the term "latent period" to define the period which in this paper is called the "initial delay." In discussing their observations, the term "initial delay" has been substituted, except in quotations, for "latent period."

First Method: After crushing or division and suture, the nerves were reexposed at various times (usually after fifteen or twenty-five days), and the distance to which regenerating axon tips had advanced was ascertained by pinching the nerve from below upward until a level was reached at which reflex responses were obtained. The presence of axon tips at this level was confirmed histologically, and the tests were so designed as to exclude the possibility of axons coming from any source other than the central stump. The distances were then plotted against times, and, on the basis of the graph thereby constructed, the authors stated:

It appears that after an initial delay in the scar the fibres advance down the nerve at a constant rate. In fact the points of Fig. 1 may reasonably be fitted by a straight line. However, since, in order to facilitate statistical comparisons, nearly all of the observations were made after either 15 or 25 days, it is not possible, from these data, to test the hypothesis that the rate of growth is constant; in all the following calculations it has been assumed to be so.

In an investigation designed to reveal the rate of regeneration, it seems premature to begin with the assumption that the rate was a constant one, and it is not unreasonable to suggest that steps should have been taken at the outset to settle this important question by making use of greater variations in the interval after interrupting conduction in the nerve.

The rate of regeneration and the initial delay, calculated by this method were, respectively, as follows: after crushing, 4.36 ± 0.24 mm. per day and 5.23 days; and after suture, 3.45 ± 0.16 mm. per day and 7.27 days.

On their graph, each point represented data provided from a single specimen, in which at least two variables were operating: (*a*) the duration of the initial delay and (*b*) the rate of advance of the axon tips (even if it is admitted, for the moment, that this remained constant for any individual specimen). Owing to the unavoidable conditions of the experiments, it was not possible for one nerve in the same specimen to provide two points on the graph.

TABLE 4.—Data Relating to Lesions of Sciatic, Medial, Popliteal and External Popliteal Nerves

Causative Injury; Nature of Nerve Lesion; Case No.		Level of Injury, Cm.	Wound Infection	Scarring	Return of Voluntary Contraction, Weeks *					
					G.	F. D. L.	F. H. L.	T. A.	P. L.	E. H. L.
Compression										
Case 188.....		Neck of fibula	+	++	21	36
245 (right leg).....		Neck of fibula	++	++	24	36
245 (left leg).....		Neck of fibula	++	++	18	30
Simple fracture of femur										
Case 326.....		10.0 above M. F. E.†	++	++	29	46	53	43	44-48	49
Gunshot wound										
Case 82.....		Head of fibula	I‡	S‡	18	35
88.....		Lower third of thigh	NII	NII	102	111
95.....		5.0 above M. F. E.	I	S	15	24	29	24	19	33
109.....		7.0 above M. F. E.	NII	NII	13	21	21	13	13	21
112.....		23.0 above M. F. E.	NII	NII	26	33	41	28	28	33
145.....		16.0 above M. F. E.	NII	NII	18	37	42	27	27	36
190.....		At M. F. E.	NII	NII	22	42	42
240.....		15.0 above M. F. E.	NII	NII	37	31	44
254.....		Head of fibula	NII	NII	7	12
Gunshot wound + bone injury										
Case 150.....		Midthigh	I	S	13	13
260.....		5.0 above M. F. E.	NII	NII	12	35	35
293.....		Midthigh	I	S	71	50	80

* G. indicates gastrocnemius; F. D. L., flexor digitorum longus; F. H. L., flexor hallucis longus; T. A., tibialis anterior; P. L., peroneus longus; E. H. L., extensor hallucis longus.

† F. F. E. means medial epicondyle of the femur.

‡ I and S denote significant infection and scarring, respectively.

On this graph, the initial, or scar, delay was calculated "as the point at which the regression line of distance traveled by the new fibers on time cuts the base-line," for calculation of which it was necessary to assume that the rate of growth was constant and the line representing it a straight one. The authors admitted that this period was not carefully determined by independent experiments. Such a calculation of the initial delay does not justify the acceptance of this figure as a constant for all specimens, nor does it seem expedient to make use of the calculation in determining the rate of growth in individual specimens. Thus, the equation

$$R = \frac{D}{T-I}$$

where R is the rate of growth; D , the distance covered by fibers; T , the duration of the experiment, and I , the initial delay, gives the rate for any specimen only if the duration of the initial delay is accurately known for that particular specimen. When values calculated from a large series of specimens (one reading only per specimen) are plotted on a graph, the growth line, whether it is straight or curved, can provide only a mean value for the initial delay and a mean value for the rate of regeneration for all the specimens contributing to its construction; from such a graph it is not possible in any particular specimen to estimate either the initial delay or the rate.

The initial delay is of particular significance in the interpretation of the data provided by each experiment. Variations in its duration are to be expected (which will influence the distance traveled by regenerating fibers down the peripheral stump in a given time), especially when the lesion is one of division and suture; it is more likely to be constant when the basis of the injury is constant (as in crushing). The following references demonstrate that the authors were aware of variations in the duration of this period:

. . . among the rabbits examined 15 days after plasma suture of the tibial or peroneal nerves, distances of outgrowth ranging from 23 to 38 mm. were recorded, with a mean of 30.1 and standard deviation of 5.3. This scatter is greater than would be expected from phenotypic and genotypic differences alone, but perhaps not more than might be expected from differences in the making of the suture [page 18].

. . . Presumably the period will vary considerably with the closeness of apposition of the stumps when the suture is made, and a large part of the variation in the distances of outgrowth recorded must be due to this cause. Indeed, it is possible to some extent to forecast from observation of the closeness of apposition at operation, whether the distance reached will be large or small. For instance, in rabbit 191 it was recorded at operation that whereas the apposition on the right side was "excellent" that on the left was "rather less successful." After 15 days it proved that fibers had reached to 38 mm. on the right but only 33 mm. on the left. Histological examinations confirmed that the union was closer on the right.

TABLE 5.—*Details Relating to Advance of Tinel's Sign and Rate of Regeneration Calculated Therefrom*

Nerve; Nature of Nerve Lesion; Case No.	Level of Lesion, Cm.*	Date of Examina- tion After Injury, Days	Level of Tinel's Sign Below Lesion, Cm.	Distance Traveled by Axons, Mm.	Time, Days	Rate of Regen- eration, Mm./Day
Median						
Suture Case 322.....	16.0 above M. H. E.	218	180	90	54	1.7
		272	270	85	114	0.7
		386	255	15	19	0.8
		405	370	60	160	0.6
		505	430			
Ulnar						
Lesion in continuity Case 24.....	At M. H. E.	39	100	170	111	1.5
			150	270		
Suture Case 105.....	25.0 above R. S. L.	71	150	100	41	2.4
	5.0 below M. H. E.	112	250			
Case 127.....	At M. H. E.	105	190	80	63	1.3
		168	270			
Case 182.....	At M. H. E.	46	130	120	63	1.9
		109	250			
Case 290.....	At M. H. E.	33	15	95	38	2.5
		71	110	180	92	2.0
		163	290	30	36	0.8
		199	320			
Case 322.....	16.0 above M. H. E.	113	200	85	54	1.6
		167	285	70	114	0.6
		281	355	15	19	0.8
		300	370	50	100	0.5
		400	420			
Sciatic						
Lesion in continuity Case 270.....	Midthigh.	258	100 †	200	124	1.6
		382	300 †	40	116	0.3
		498	340 †			
Suture Case 94.....	20.0 above M. F. E.	108	280	160	98	1.6
		206	440	50	42	1.2
		248	490	30	42	0.7
		290	520	110	222	0.5
		512	630			
Case 122.....	36.0 above M. F. E.	129	280	260	121	2.1
		250	540	100	70	1.4
		320	640			
Case 137.....	2.0 above M. F. E.	140	300	270	106	1.6
		306	570			
External popliteal						
Lesion in continuity Case 174.....	Neck of fibula	337	150	70	98	0.7
		435	290			

* M. H. E and R.S.L. denote medial epicondyle of humerus and level of styloid process of radius, respectively.

† Measurements taken from the head of the fibula.

Referring to the results following suture of the sciatic nerve in the dog, they stated:

The delay in the scar cannot have been less than 8 days, and may have been more, since the junction was not a very satisfactory one, so the rate of growth of the fibers must have been at least 2.3 mm./day.

In any case we may conclude that, as with sensory fibers, the rate is lower, and the latent period longer, after cutting and suturing the nerve than after interruption by crushing.

Elsewhere, however, the initial delay was regarded as a constant. Thus, referring to the scatter in the estimates for distances, they concluded that "it is individual differences in the rate of regeneration rather than in the latent period that is responsible for the scatter of the estimates." Again, they stated that, after crushing, "the distances reached are considerably greater than those which would have been found after complete severance and suture of the nerve, although, as already mentioned, the latent period is hardly different in the two cases. In fact, the greater distances reached after the operation of crushing are due to the faster growth of fibers in the peripheral stump."

In view of these conflicting statements, it is difficult to ascertain the precise views of the authors on the initial delay. It would appear, however, that both the initial delay and the rate of growth show individual variations.

Second Method: The peroneal nerve in the rabbit was crushed at various levels in different specimens. The distance from the lesion to the lowest point of the analgesic area of the foot, together with the time taken for pain sensibility to reappear at this point (as indicated by the ability to elicit reflex responses by the application of painful stimuli), was recorded for each lesion.

From these data a graph was constructed, from which a rate of growth of 3.04 ± 0.35 mm. per day and an initial delay of 9.8 days were calculated. As already pointed out, data treated in this way can provide only mean values for the rate and the initial delay, and these should not be used for calculating values in individual specimens. This point is further illustrated by a separate account of the results in 4 of the experiments, in which the nerves were crushed at different levels on the two sides of the same animal. The rates ranged from 3.03 to 3.95 mm. per day, with a mean of 3.39 mm., and the initial delay varied from 12.7 to 29.2 days, with a mean of 19.0 days. Thus, even with a crush injury, in which the lesions might reasonably be expected to be comparable over a series of animals, the initial delay varied from 12.7 to 29.2 days. It would seem futile, therefore, to postulate a constant initial delay in calculating the rate in any one case.

The rate was slower in the experiments devoted to a recording of recovering sensation. To explain this, it was suggested that the rate of advance of maturation was being measured. There is, however, no

evidence that this was the case. On the application of a painful stimulus to the skin, the presence of immature fibers is sufficient to provide the basis for reflex activity. A similar response follows both pinching the exposed nerve and application of a painful stimulus to the cutaneous area, and the impulses in both experiments could be transmitted by fibers showing similar morphologic features; in one set of experiments the impulses were shown to arise in bare axon tips. A significant difference in the two experiments, however, was that effects of pinching the nerve were recorded within twenty-five days, while pricking the skin did not elicit a response until from sixty-seven to one hundred and one days after the nerve was crushed, by which time the fibers had covered much greater distances. Furthermore, the reinnervation of skin involves additional and complicated changes in the superficial cutaneous plexuses.

As an alternative explanation of the slower rate, it could be argued that since the distances to be covered were much greater and the duration of the experiments was longer the rate in the later stages may have slowed down, thereby resulting in a slower average rate for the duration of the experiment and the distance over which it was measured. The suggestion of a progressively diminishing rate as recovery proceeds is, of course, in conflict with the basic assumption of the authors that the rate is constant.

Third Method: The rate was measured at which a denervated cutaneous area diminished during the reappearance of pain sensibility which was sufficiently intense to elicit reflex responses; the possibility of overlap from adjacent cutaneous nerves was excluded.

Gutmann and his associates regarded this process as an example of the "advance of functional completion of sensory nerve fibers"; they failed to exclude the possibility, however, that the presence of immature fibers may be sufficient to permit the elicitation in the animal of those responses which are thought to signify sensory recovery. The rate of shrinkage was 2.05 ± 0.14 mm. per day after crushing and 1.57 ± 0.15 mm. per day after suture. Presumably, the range over which the rate varied was again calculated on the basis of a constant initial delay.

To account for the low rate, two explanations were offered: (1) the distance between two points on the surface of the skin does not represent the whole of the distance that the nerve fibers must travel before the advancing edge of sensitivity moves from one point to another; (2) the regenerative processes may proceed more slowly in the ultimate plexus than in the main nerve trunk.

Fourth Method: The peroneal nerve was crushed, or severed and sutured, at various levels in different specimens and the time recorded at which motor recovery made its first appearance. The criterion of returning motor function was the reflex spreading of the toes which

occurs on suddenly lowering an animal held by "the scruff of the neck." The distances from the lesions to the muscles responsible were obtained by direct measurement along the nerve, though the distal end point was not given. In this test, it is the recovery of muscles to a stage at which they are able to participate in reflex activity that is being examined. Though it was claimed that reflex activity of this type is an indicator of conduction which is dependent on the matured fiber, there is no convincing evidence that such activity demands a degree of maturation commensurate with that required for the restoration of functionally effective voluntary activity.

A graph was constructed from the observed times and distances, and from these data were calculated a rate of growth of 3.05 ± 0.14 mm. per day and an initial delay of 20.8 days. The error of using a mean value for the initial delay in calculating the rate in an individual specimen has already been pointed out; it is further illustrated by the results in 4 specimens in which the nerve had been crushed high on one side and low on the other. The rates ranged from 2.86 to 3.29 mm. per day, with a mean of 3.1 mm.; and the initial delay varied from 20.41 to 22.52 days, with a mean of 21.6 days. Another series of experiments, in which the nerves were severed and joined with plasma, gave a rate of 2.02 ± 0.3 mm. per day and an initial delay of 32.3 days. In 4 animals the nerve was cut and joined high on one side and low on the other. The rates ranged from 2.17 to 2.93 mm. per day, with a mean of 2.6 mm.; and the initial delay varied from 29.8 to 42.5 days, with a mean of 36.5 days.

The slower rate obtained with this method was explained on the supposition that it was the rate of advance of maturation that was under review. The experiments, however, involved longer distances and greater times than those designed to reveal the rate of advance of axon tips, and it is believed that the over-all slower rate is more satisfactorily accounted for by a progressive diminution in the rate with the advance of repair.

In applying this method for estimating rates, it was assumed by the authors that in two given muscles there would be no significant variation in the terminal delay. They designed control experiments in order to detect any possible error in this connection.

In 3 rabbits the nerve was crushed high on one side and low on the other. About the time when it was calculated that regenerating motor fibers from the proximal lesion on one side would have reached the level of the distal lesion on the other, the lower lesion was recreated by crushing the nerve again at the old site. In this way it was hoped to insure that the regenerating fibers from different levels would reach muscles which had been denervated for the same period. A comparison of the results of this set of experiments with the results given

by the experiments in which the nerves were crushed only once led the authors to state that "it is perhaps just suggestive of a prolongation of the period of delay with progressive atrophy of the muscle." Three possible sources of error in the control experiments were considered:

(1) . . . After the second interruption the outgrowth of fibers might be less (or conceivably more) vigorous than after an initial lesion. But in other experiments (Holmes & Young) the outgrowth has been found to be at all times equally vigorous under such conditions. (2) The scar resulting from the first operation might delay the fibers. Other experiments in which high rates of growth have been observed through much more seriously scarred nerves show that this is unlikely. . . . (3) Since the distance between the two lesions was greater than that of the lower one from the muscle it is clear that for a few days before the second operation axon tips must have been present in the muscle on the low-operated side, and might possibly have had some effect on the condition of the muscle fibers.

Other possible sources of error which were not mentioned are:

1. Since it is impossible to forecast accurately the rate and initial delay for any individual specimen, there is a very wide range of variation in the time when the fibers from the proximal lesion would reach the level of the distal lesion; there is, consequently, no assurance that the distal lesion will be renewed at the appropriate time.
2. No account was taken of the initial delay—which may vary greatly—occurring after the second crushing.
3. In the event of the rate of growth not being constant, a further source of error is introduced.

For these three reasons, the control experiments are unlikely to provide the desired information.

Fifth Method: The rate of growth of functionally mature motor fibers was calculated from the distance between two muscles and the interval between the times of their recovery. The times were recorded at which reflex spreading of the toes and dorsiflexion of the foot were elicited by pricking the sole. The distance between the two muscles concerned was not measured in the 6 specimens studied, however, but was obtained from 2 others. This method of testing the return of muscle function again throws doubt on the validity of the assumption that it is the advance of maturation which is being measured.

The estimated rate of advance of "functional ability" was 2.2 mm. per day, while in 1 case of suture the rate of 1.2 mm. per day was recorded. These figures were regarded as "at best a very rough approximation," and the method was dismissed as unsuitable.

Conclusions: This somewhat detailed examination of the experimental investigations of Gutmann and associates²⁸ has been necessary because, despite their comprehensive treatment of the problem and the acknowledged value of their contributions, the investigations fail to

provide entirely satisfactory evidence and raise certain objections of a highly significant nature; there is, however, justification for the claim that the rate following suture is slower than that following crushing. These objections may be stated as follows:

1. Their calculations are based on the assumption, for which there is no justification, that the rate is constant. This is, in itself, a fundamental weakness in an investigation designed to reveal the rate.

2. It is significant that, owing to the unavoidable conditions of the experiments, the distances and times were provided by single observations on each of a number of nerves in a series of rabbits—in only one method (the fifth) could a single nerve provide two readings, and this method was dismissed as unsuitable. For this reason, it was impossible to calculate either the rate or the initial delay in any individual specimen—the most that could be expected of the methods would be a mean rate distributed over all the specimens. From this information it is possible to calculate an average initial delay; but since this period has been shown to vary, it could not be usefully employed for calculating the rates in individual specimens.

3. It would appear that in all their experiments the authors were testing reflex activity. In four of the methods it was claimed that it was the "advance of functional completion" of motor and sensory nerve fibers which was being measured, and that reflex activity of the type employed was an indicator of conduction through a fully matured nerve fiber. There is, however, no convincing evidence either that such activity depends for its expression on a completely matured axonal pathway or that it is not as efficiently served by an immature axon soon after reaching its end organ. As a result, the relationship between the rate of advance of axon tips and that of full maturation remains uncertain.

4. There is ample evidence of a considerable range of variation in the initial delay. Opposed to this is the repeated assumption (on which calculations are based) that this period is constant.

5. The growth of axon tips was studied for shorter times and over shorter distances than was the rate of "advance of functional completion." The difference in rates was attributed to differences in the structure of the conducting fiber. There are, however, cogent reasons for attributing, in part at least, the higher rate in the former to the short duration of the experiments and for believing that in the latter the rate had had time to slow down. This, in turn, implies a progressive diminution in the rate as regeneration advances.

6. Considerable limitations are imposed by animal experimentation with reference to the extension of the observations to clinical neurology.

(a) The distances over which the process can be traced are very short as compared with those in man.

(b) In animals it is not possible to apply tests which depend on voluntary control and on the transmission of sensory impulses which will permit their correct interpretation.

Ramón y Cajal.—Ramón y Cajal⁷ demonstrated "from numerous measurements in rabbits, cats and dogs whose sciatic nerve was completely cut across" that "the velocity of the cones of growth in the peripheral stump is between 2 and 3 mm. in 24 hours. . . . In some really exceptional cases the velocity of growth was 4 mm. per day." Individual data, however, were not given, nor were his methods detailed.

CLINICAL METHODS

The difficulties experienced in accurately estimating rates of recovery in human peripheral nerves are considerable since only a small proportion of a large series of cases will provide the data which are essential for the calculation of the rate. Thus, of 500 cases at the Oxford Centre, Seddon, Medawar and Smith^{2b} found only 33 suitable for this purpose (25 for the study of motor and 4 for the study of sensory recovery, and 4 for calculating the rate of advance of Tinel's sign). In a series of 301 cases, I had 50 nerve injuries (13 of the radial, 21 of the ulnar and 16 of the sciatic nerve) suitable for calculation of the rate of regeneration of motor fibers and only 13 in which the rate of advance of Tinel's sign could be estimated. References to the rate of recovery by other investigators⁸ are not sufficiently detailed to be of value.

Seddon, Medawar and Smith.^{2b}—These investigators employed three methods for calculating the rate.

1. The times of the reappearance of voluntary contraction were charted against the distances from the site of the lesion to the muscles. From the graph thereby constructed they calculated (1) "the rate of advance of the wave front of functional maturation" and (2) the initial delay, which was obtained by projecting the line representing the growth rate so as to intersect the basal line of time.

"In most of our cases," said the authors,^{2b} "the assumption that the rate of recovery is *constant* over the range of times and distances within

7. Ramón y Cajal, S.: *Degeneration and Regeneration of the Nervous System*, London, Oxford University Press, 1928, vol. 1.

8. (a) Tinel, J.: *Nerve Wounds*, London, Baillière, Tindall & Cox, 1917. (b) Dustin, A. P.: *Les lésions post traumatiques des nerfs: Contribution à l'histopathologie du système nerveux périphérique chez l'homme*, Ambulance de l'océan 1 (pt. 2):71-161, 1917. (c) Marble, H. C.; Hamlin, E., Jr., and Watkins, A. L.: *Regeneration in the Ulnar, Median and Radial Nerves*, Am. J. Surg. 55:274-294 (Feb.) 1942.

which the readings lie gives a very satisfactory approximation to the data," although there were "remarkable variations in rate, even for lesions of the same nerve and, if anything, even greater variations in the 'latent periods.'" The results in 7 of these cases were unusual in that the initial delay, as calculated by extrapolation, fell on the negative side of the time axis. To account for this, it was assumed that in the initial stages the rate must have been much greater than that calculated; this, in turn, invalidated the method for obtaining the initial delay, even when this had been shown to have a positive value, and led to a final pronouncement that "there will be no temptation to estimate the latent period by extrapolation." This assumption of a diminishing rate was supported by the findings in 3 cases, from which a curve of growth was obtained. From a detailed mathematical analysis of the findings in these 3 cases, it was inferred that "the rate of regeneration is initially as high as 3 mm. a day, and that it falls off progressively down to and then below a value of the order of 1 mm. a day about 100 days after recovery has started."

These conflicting results were reconciled by suggesting that, though the rate falls off progressively over the whole period of recovery, it may reasonably be assumed to be constant over "moderate ranges of time and distance" at the following average estimates: (1) in the radial nerve: (a) after suture: 1.6 ± 0.2 mm. per day; (b) after axonotmesis: 1.5 ± 0.1 mm. per day; (2) in all nerves studied: (a) after suture: 1.5 ± 0.2 mm. per day; (b) after axonotmesis: 1.4 ± 0.1 mm. per day.

The term "moderate ranges of times and distance" was not qualified, though the diminishing rate was assigned to the phase before "the range of times and distances accessible to measurement" (that is, preceding the onset of recovery) and to the later phases in a few cases in which the regenerative process was spread over a long period. The moderate ranges of distance, therefore, must have been the difference between the measurements to the first and the last muscle innervated, while the range of time would be the period intervening between the reappearance of contraction in the same two muscles. From the included graphs, this period appears to have commenced at about one hundred days and to have extended over the next one hundred to two hundred days. It had previously been inferred from the curved graphs, however, that the rate would fall below the order of 1 mm. per day about one hundred days after recovery had started, and presumably this recovery meant the first reappearance of voluntary contraction. From this it can only be assumed that over "the moderate ranges of times and distance" the rate could not be constant at the average estimates given.

Another error was introduced into the calculations of Seddon, Medawar and Smith by their acceptance of values, in which no account was taken of any variation, for the distances between the bony landmark

and the muscle innervated. The distance to any individual muscle varies greatly in different subjects, but the authors used a constant value, based, it would appear, on an average obtained from a number of cases. In this they were undoubtedly misled by the anatomic data at their disposal. In the construction of their graphs, therefore, the figures on the distance axis are based not on measurement but on assumption, and their possible inaccuracy may explain the negative initial delay obtained in their graphs. Thus, instead of the fibers advancing at a much greater rate in the early stages, it is conceivable that they had shorter distances to cover before innervating the muscles; this could sufficiently depress the growth line to carry its projection onto the positive side of the time axis.

2. The rate of advance of axon tips was calculated on the basis of an advancing *Tinel* sign. Observations were made on 6 nerves of 4 patients after suture. The rates of recovery varied from 1.37 to 2.25 mm. per day, with an average of 1.71 mm. In 5 of the cases a negative initial delay was obtained by projection of the straight line of growth obtained in the graph. Readings in the earlier stages of recovery would have corrected this, but in one of the graphs (fig. 8) there is sufficient evidence to indicate a falling off of the rate over the period for which the observations were conducted. The data included in this graph, however, were confusing in that a comparison of the fourth and fifth readings for the ulnar nerve and the fifth and sixth readings for the median nerve show a regression, and not a progression, of *Tinel*'s sign. An examination of all the data provided would not support their assumption that the rate, as represented by the growth line in the graphs, is constant.

3. The rate of regeneration was estimated by following the retrogression of the upper margin of an elongated zone of cutaneous sensory loss during recovery. This is the clinical equivalent of the third method employed by Gutmann and associates.^{2a} The recovery of pain and touch sensibility was followed in 4 patients, and the conditions of the investigation were apparently such as to insure that the advance of functional maturity was being measured. Rates varying from 0.78 to 1.28 mm. per day were obtained, with a mean of 1.08 mm. As pointed out by the authors, the cases were not numerous enough to warrant discussion, though they form a guide to the rate at which the completed process advances in the cutaneous plexuses.

Sunderland.¹—Two methods were employed to calculate the rate and to ascertain whether or not it was constant and, if not constant, to determine the manner and extent to which it varied.

First Method : After injury of a nerve, with or without suture, the rate of advance of *Tinel*'s sign (which is thought to signify the location of sensory axon tips) was calculated over various segments

of nerves and at different stages of recovery (table 5). After suture, regenerating sensory fibers advanced down the forearm and leg at a progressively diminishing rate, which in the initial stages might be as great as 3 mm. a day for the forearm and 2 mm. for the leg. The rate then slowed until it reached a value of approximately 0.5 mm. per day at the wrist and ankle.

Second Method: With this method, the details of which are provided in an earlier paper,^{1a} the rate of advance of functionally mature motor fibers was calculated over successive segments of a nerve by the use of the formula:

$$R = \frac{L^2 - L^1}{T^2 - T^1}$$

where L^1 and L^2 are the shortest distances to two muscles from a point on the nerve proximal to the site of origin of its first branch. Values for these lengths were provided by preliminary anatomic investigations* (table 1).

T^1 and T^2 signify the duration of the time, in days, between the date of the injury (or suture) and the date of recovery in the two muscles. These values were obtained from clinical observations on patients with peripheral nerve injuries. To qualify for selection, a case had to fulfil the following conditions:

1. Interruption of conduction must be complete and associated with wallerian degeneration.
2. The onset and progress of recovery must be such as to suggest uniform involvement of fibers at the site of injury.
3. The onset and progress of recovery must be such as to suggest that the axons had commenced to regenerate at about the same time.
4. Any departure from the normal order of recovery of muscles should be capable of satisfactory explanation on the basis of established anatomic variations in innervation.
5. In order to detect the earliest signs of recovery in individual muscles, the patients had to be examined at intervals not exceeding a week until all the muscles were contracting.

The accuracy of the formula depends on the following assumptions:

1. That the delay at the site of injury is the same for regenerating axons destined for the two muscles. There can be no certainty of this after suture, but in axonotmesis this factor can be controlled by the careful selection of cases.
2. That the intramuscular distance to be covered before the reestablishment of neuromuscular relations is the same within each muscle. Anatomic investigation has shown that the intramuscular length of the fibers was proportional to the size of the muscles and was approximately the same in muscles of comparable dimensions.

3. That, in the two given muscles, there is no significant difference in the terminal delay. In order to reduce this possible source of error to a minimum, the rate was calculated independently over several short segments of the nerve. This meant that there was no great difference between the length of time for which the two muscles were denervated.

4. That in the same segment of nerve there is no difference in rate between fibers destined for the two muscles and that there is no significant diminution in rate over the additional distance to the more distal muscle. Since the rate normally diminishes as the axons advance, this formula should not be employed when a considerable distance separates the muscles; selection of suitable muscles enables the rate to be calculated over several short sections of the nerve.

The method has the following advantages:

1. It renders unnecessary a knowledge of the level of the injury, since the distance along the nerve to the origin of the proximal branch is common to the measurement for each muscle.

2. It renders unnecessary a knowledge of the initial delay at the site of the lesion. This is especially convenient, since in each individual case the delay cannot be estimated with any degree of accuracy.

3. By selecting muscles innervated at different levels, the rate of regeneration can be estimated over different segments of the nerve. By this means it can be ascertained whether or not regeneration proceeds uniformly during the entire process, though the rate cannot be estimated in the section between the level of injury and the origin of the first branch.

The rate of regeneration can be estimated in any individual case, or an average rate, calculated from the average readings for $T^2 - T^1$, can be obtained from observations on several patients. In an individual case it is necessary to take into consideration the unpredictable range of variation, from subject to subject, in the length of the shortest fibers to any given muscle. When mean readings for $L^2 - L^1$ and $T^2 - T^1$ are obtained from a number of cases (as in the present inquiry), it is believed that this unpredictable element is reduced to a minimum. By taking average values for $L^2 - L^1$ and $T^2 - T^1$, factors are disregarded which are peculiar to an individual subject and which may influence the rate. Regardless of the method employed, however, the rate in any individual case can be calculated only in retrospect—that is, after regeneration itself has rendered available the figures for T^1 and T^2 , and even then the figures for L^1 and L^2 must be average values obtained from the cadaver, for there is no way of obtaining this information in the living subject. For these reasons, an average estimate only has been sought, which, in view of the possible sources of

error, can make no claim to great accuracy. In this connection one was influenced by the warning of the late Wilfred Trotter⁹:

Results: Calculations for the radial, ulnar (in the hand) and sciatic nerves have already been made available.^{1a, b} Seven cases of suture of the ulnar nerve have now accumulated in which it was possible to measure the time taken to travel the length of the forearm (table 3, cases 100, 158, 183, 207, 246, 277 and 290) and, from this information, to calculate the rate for this section of the nerve. The distances involved, however, were greater than those for which the method was designed. Though no great accuracy, therefore, is claimed for the results, they at least provide a guide to the mean rates for the length of the nerve in the forearm, which for the cases, in the order stated, were: 1.0, 0.6, 1.0, 0.7, 1.0, 1.0 and 0.6 mm. per day. Furthermore, the results were such as to justify the conclusion that the rate in the forearm was greater than that in the hand.

For the entire series, the mean rates, in millimeters per day, were as follows:

After axonotmesis

Radial nerve: 1.9 mm. for segments about the elbow
0.8 mm. for segments in the midforearm

Ulnar nerve: 0.6 mm. for the terminal section in the hand

Sciatic nerve: Diminution in rate from 2 to 1 mm. per day over the popliteal divisions in the region of the knee and the upper half of the leg

After suture

Radial nerve: 1.2 mm. for segments about the elbow
0.6 mm. for segments in the midforearm

Ulnar nerve: 0.8 mm. when measured over the entire length of the nerve in the forearm

0.4 mm. for the terminal section in the hand

General Conclusions Based on Personal Observations.—1. The suggestion,¹⁰ based on experimental studies, "that there is not likely to be a decline in the rate of growth of fibers in the distal portions of long nerves, such as those of man" is not supported by the findings in this investigation.

There is, on the other hand, convincing evidence that the rate of advance of both the axon tips and the process of functional maturation diminishes progressively over the whole period of recovery and should not be regarded as constant for any phase of the process. This is not surprising, for a steadily diminishing rate is characteristic of most growth processes.

9. Trotter, W.: *Collected Papers*, London, Oxford University Press, 1941. The affectation of scientific exactitude in circumstances where it has no meaning is perhaps the fallacy of method to which medicine is now most exposed.

10. Young, J. Z.: *The Functional Repair of Nervous Tissue*, *Physiol. Rev.* 22:318-374 (Oct.) 1942.

2. The axon tips advance with a greater velocity than does the process of functional completion.

3. The rate for any particular segment of the nerve depends on its distance from the parent neurons and is not affected by the level of the injury, though the latter is all-important in fixing the initial velocity of regeneration. Thus, the initial rate is faster when the lesion is close to the cell bodies and slower when the lesion is more remote. In the former case, the rate slowly diminishes and, on reaching the more distal level, approximates the commencing rate of regeneration for a lesion in that segment.

4. There is evidence that the rate of regeneration following axonotmesis is greater than that following suture for all sections of the nerve. The difference is greater proximally; over the terminal portion of the nerve the rates appear to approximate. From the data available it is not possible to ascertain precisely the extent to which the rate is slower after suture.

5. After axonotmesis, the rate of advance of functional maturation over the proximal portion of the nerve, in the upper part of the arm and thigh, is probably in the vicinity of 3 mm. per day and slowly diminishes to approximately 0.5 mm. per day over the distal portion, in the hand and foot.

6. After suture, the axon tips advance down the forearm and leg at a rate, in the vicinity of the elbow and knee, of approximately 3 and 2 mm. per day, respectively, but which gradually slows until, at the wrist and ankle, it is commensurate with that observed for functional completion.

7. The observation that the rate is greater after axonotmesis than after suture suggests that there are factors which can influence it.

8. Two factors which greatly influence the result operate in any calculation of the rate: (a) the length of nerve over which the rate is calculated and (b) the level of the segment of the nerve over which the rate is measured.

ADVANCE OF AXON TIPS AND MATURATION OF NERVE FIBERS

After a nerve injury which results in wallerian degeneration, anatomic repair is directed toward (a) reconstituting the axonal pathway between the central stump and the peripheral end organ, and (b) converting the axon into a functionally mature nerve fiber, on which depends its capacity either to conduct an impulse initiated by the cerebral cortex or to transmit sensory impulses which can be correctly interpreted.

Functionally effective repair implies such additional factors as (a) the reestablishment of old relations with the end organs without distortion and in sufficient numbers to permit the action of fibers in groups large enough to provide for integrated and controlled activity, and (b) subsequent to the reestablishment of simple anatomic continuity, the restoration of the end organ to a state fit for functioning. It is not proposed to consider any local factors at the site of injury which may influence the restoration of the fiber pattern; though the reestablishment of correct relations between the nerve cell and the peripheral end organ depends on these factors, they do not fall within the scope of the present inquiry. In any case, these considerations do not apply in axonotmesis, since in such injuries the fiber pattern is fully preserved.

There is evidence that the restoration of function does not follow immediately on the reestablishment of anatomic continuity between the central stump and the end organ. Thus, electromyographic responses typical of reinnervated muscle can be obtained from paralyzed muscles prior to the reappearance of voluntary contraction.¹¹ This feature is illustrated in 3 cases in my series.

CASE 176.—A. M. T. sustained a perforating gunshot wound of the left forearm on Dec. 27, 1942, which resulted in complete interruption of conduction in the ulnar nerve below the branches to the flexor carpi ulnaris and flexor digitorum profundus muscles. The wounds healed without any complications; a tender swelling developed on the nerve beneath the wound of entry at the level of the mid forearm. The lesion of the ulnar nerve was still complete two hundred and seventeen days after the injury, when the nerve was explored (Major H. Trumble). The small swelling on the ulnar margin of the nerve was only lightly adherent to neighboring structures. Direct stimulation of the nerve above the bulb resulted in slow, wormlike contractions of the hypothenar muscles. The strength of current required to elicit these responses was greater than that required to elicit a similar response from neighboring muscles innervated by the median nerve. In view of this conduction, the wound was closed without disturbing the nerve. Voluntary contractions returned in the hypothenar muscles a week later and in the first dorsal interosseous muscle in seven weeks after that. The patient subsequently made a recovery which was judged just short of normal; residual motor disability was due to injuries to the metacarpal bones received at the time of the original injury.

CASE 231.—J. W. A. sustained a perforating gunshot wound of the right arm on Aug. 24, 1943, resulting in a comminuted fracture of the midthird of the shaft of the humerus. There was extensive injury to soft tissues, and the field notes stated: ". . . the radial nerve was torn and a piece blown away. The proximal end was lying in the wound and terminated at the level of the upper end of the humerus." Fifteen weeks after the injury there was a complete lesion of the nerve involving the brachioradialis muscle and the posterior cutaneous nerve of the forearm. Because of infection, exploration (Major H. Trumble) was delayed until twenty-six weeks after the injury. Local scarring was considerable. The

11. Weddell, G.; Feinstein, B., and Pattle, R. E.: The Electrical Activity of Voluntary Muscle in Man Under Normal and Pathological Conditions, *Brain* **67**: 178-257 (Sept.) 1944.

nerve was exposed in the middle and distal thirds of the arm; it had not been severed and was not involved in scar tissue. Electrical stimulation produced weak contraction of the brachioradialis. The strength of current required to elicit this response was greater than that required to elicit a similar response from normal muscle. Since spontaneous regeneration apparently was taking place, the nerve was left undisturbed and the wound closed.

Voluntary contraction did not appear in the brachioradialis until forty weeks after the injury, that is, fourteen weeks after a response had been obtained by electrical stimulation of the nerve. Recovery then proceeded uninterruptedly and in anatomic order until, at the end of fifty-six weeks, all muscles were contracting. The power steadily improved until, at the end of seventy-seven weeks, all movements could be performed against resistance and the power of the grip was one third that on the opposite side. At this stage there had been slight improvement in cutaneous sensation.

CASE 237.—S. C. sustained a perforating gunshot wound of the left forearm on Dec. 8, 1943, which resulted in complete interruption of conduction in the ulnar nerve. A fusiform swelling appeared on the nerve beneath the scar of entry, 8 cm. above the distal crease in the wrist. There appeared to be some recovery of sensation at the base of the hypothenar eminence one hundred and twenty-five days after the injury; there was no further improvement. The nerve was explored by Major H. Trumble one hundred days later. It was observed to enter scar tissue 8 cm. above the distal crease in the wrist and was there bound to the neighboring tissues. Within this scarred zone the nerve was expanded for about 1 inch (2.5 cm.) into a fusiform swelling, which showed a transverse constriction at its middle. Stimulation of the nerve above the bulb gave weak contractions of the intrinsic muscles of the hand and of the ulnar half of the flexor digitorum profundus muscle. Apparently, a branch proceeded to the deep flexor muscle from the scarred segment of the nerve. The strength of current required to elicit these responses was greater than that required to elicit a similar response from neighboring muscle innervated by the median nerve. The wound was closed without freeing the neuroma.

Thirteen days later feeble voluntary contractions were first observed in the hypothenar muscles—an additional eight weeks elapsed before contractions appeared in the first dorsal interosseous muscle. The end result was assessed as just short of normal.

At least three factors must be presumed to be responsible for the delay between the reestablishment of anatomic continuity and the onset of voluntary contraction: (1) changes in the structure of the nerve fiber leading to functional maturation, (2) analogous change at the end organ leading to effective union with muscle fibers, and (3) (probably) a minimum number of mature fibers must be present before voluntary contraction appears. But, in the absence of histologic examination of the nerve fiber and the end organ during the crucial period of recovery, it cannot be determined in what proportion these factors are responsible.

Myelination and the restoration of fiber diameter are known to influence conduction, and there is ample evidence that these processes advance down the distal stump at a later date than does growth of

the axon tip.¹² According to Ramón y Cajal,⁷ "growth in diameter continues long after the appearance of the medullary sheath." Other factors of a more subtle character must also be taken into account. Thus, in the nerve lesions of the type defined by Seddon as neurapraxia, there may be complete interruption of conduction without Wallerian degeneration or any significant morphologic change in the fiber (Denny-Brown and Brenner,¹³ Weiss and Davis,¹⁴ Seddon,¹⁵ Sunderland¹⁶).

The rate of regeneration, as calculated by Gutmann and associates,^{2a} varied according to the method used; this difference the authors attributed to the difference in the structure of the conducting fiber at different stages. The "pinch" method, which gave a faster rate, was shown by histologic examination to be applicable to axon tips. The other methods, however, depended on reflex activity, and the slower rates obtained were attributed to a presumed necessity for fully matured fibers. There is no convincing evidence, however, either that such reflex activity depends on a completely matured pathway or that it is not as efficiently served by an immature axon. In their experiments the growth of the axon tips was studied for shorter times and over shorter distances than was the rate of "advance of functional completion." Clinical observations indicate that the rate of regeneration is high at first and decreases later. In the animal experiments the rate was calculated for axon tips during brief periods at the beginning of growth, when the rate is most rapid. The higher rate for the axon tips is therefore not surprising; had the experiments been prolonged, it probably would have decreased and given a slower over-all rate.

It is generally accepted that Tinel's sign provides evidence of the presence of "young axis-cylinders in the process of regeneration," though there has been no histologic confirmation of this. Assuming this to be so, an advancing Tinel sign may be employed for determining the rate of advance of bare axons. Seddon, Medawar and Smith^{2b}

12. Howell, W. H., and Huber, G. C.: A Physiological, Histological and Clinical Study of the Degeneration and Regeneration in Peripheral Nerve Fibers After Severance of Their Connections with the Nerve Centers, *J. Physiol.* **13**: 335-406, 1892. Lewis, D., and Kirk, E. G.: Regeneration of Peripheral Nerves: An Experimental Study, *Tr. Am. S. A.* **34**:486-536, 1916. Sanders, F. K., and Young, J. Z.: The Degeneration and Reinnervation of Grafted Nerves, *J. Anat.* **76**:143-166 (Jan.) 1942. Weddell and others,¹¹ Ramón y Cajal.⁷

13. Denny-Brown, D., and Brenner, C.: Paralysis of Nerve Induced by Direct Pressure and by Tourniquet, *Arch. Neurol. & Psychiat.* **51**:1-26 (Jan.) 1944.

14. Weiss, P., and Davis, H.: Pressure Block in Nerves Provided with Arterial Sleeves, *J. Neurophysiol.* **6**:269-286 (July) 1943.

15. Seddon, H. J.: Three Types of Nerve Injury, *Brain* **66**:237-288 (Dec.) 1943.

16. Sunderland, S.: Traumatic Injuries of Peripheral Nerves: I. Simple Compression Injuries of the Radial Nerve, *Brain* **68**:56-72 (March) 1945.

expressed the belief that "the wave front for Tinel's sign should . . . be well in front of that for motor and sensory fibers that have advanced to functional maturity." This, however, was not supported by their results, since they found that after suture axon tips advanced at an average rate of 1.71 mm. per day, while the rate of advance of functional maturity, based on the return of contraction of voluntary muscle after suture, was 1.6 ± 0.2 mm. per day. In a previous paper,^{1e} I presented data from which it was tentatively inferred that the rate for an advancing Tinel sign did not differ significantly from that provided by a study of voluntary motor function. At that time due weight was not assigned to two factors which the accumulated evidence has now shown to be all-important in affecting a comparison of the rates. These, as will be demonstrated in a subsequent section, are: (1) the length of nerve over which the rate is measured, and (2) the levels at which the measurements are taken.

A more detailed analysis of the data (table 5) on this basis has shown that the rate of advance of the bare axon is well in advance of the rate of functional maturation; this was more apparent in the cases in which both Tinel's sign and the return of voluntary contraction could be observed in the same subject (case 290, tables 3 and 5).

Conclusion.—From an analysis of all the information, it is evident that the regeneration of the axon and the maturation of the axonal pathway, on which the restoration of function depends, occur as two separate events in the process of repair. Maturation involves further morphologic changes of a complex character, such as myelination and the restoration of the fiber diameter, which proceed at a slower rate than does the advance of the bare axon.

FACTORS RESPONSIBLE FOR INDIVIDUAL VARIATIONS IN RATE OF REGENERATION AND FOR ITS PROGRESSIVE DECLINE THROUGHOUT THE PROCESS OF REPAIR

The rate of regeneration of nerve fibers is controlled by a number of factors which lead to individual variations, but it seems to be a general rule that the rate diminishes progressively in any one case. The capacity of the neuron to reform the injured fiber and the progress of the axon tip along the peripheral stump are the result of the combined action of two forces:

1. The activity of an especially organized growth cone, constituting the axon tips, which, as it descends, leads to the elongation of the axoplasm. Though localized at the extremity of the process, this activity requires for its effective control dynamic impulses from the cell body. This factor accounts for the multiple exploratory prolongations which sprout from each axon tip during regeneration and for the manner in which each seeks the path of least resistance distally, though this

also appears to be influenced mechanically by tissue lines of stress.¹⁷ When the axon tip finds a suitable pathway, it progresses at a rapid rate. The most suitable pathway is that provided by the neurilemmal tubes, and there is some evidence that axons seek Schwann cells in preference to all other tissues. This should not be surprising in view of the fact that a covering of these cells is essential for the proper functioning of all peripheral nerve fibers. The recent observations of Denny-Brown¹⁸ suggest that the cells which ensheathe the newly formed axons are not mature Schwann cells but the neural fibroblasts which abound as the result of the proliferation of the connective tissue cells of the perineurium and endoneurium and which, by flattening themselves around the axis-cylinders, become Schwann cells.

2. Central changes in the cell which propel the axon tip distally. This factor has been recognized by a number of authors under different names—the law of continuous growth of His¹⁹ and Ramón y Cajal⁷; the *vis a tergo* of Held²⁰; the axonal turgescence of Dustin^{17c}; the histodynamic impulse of Heidenhain,²¹ and the turgor pressure of Young.²² More recently, Weiss and Taylor²³ have reported observations which suggest that "a growing fiber requires continuous contributions from its central cell body, the throttling of which entails a corresponding reduction of growth and myelinization."

Connection with the cell body is a prerequisite on which the life of the fiber depends, and the transmission of the vital impulse appears to be associated with an appreciable intracellular pressure. That this pressure is appreciable is suggested by the outflow of axoplasm when the fiber is severed and by the herniation of the intrafunicular contents when the perineurium is breached. The endoneurium is very thin and, alone, would have difficulty in withstanding the lateral thrust of the intracellular factor. In order to compensate for this weakness, the

17. (a) Ranvier, L. A.: *Leçons sur l'histologie du système nerveux*, Paris, F. Savy, 1878, vol. 2. (b) Vanlair, cited by Ramón y Cajal.⁷ (c) Dustin, A. P.: *Le rôle des tropismes et de l'odogenèse dans la régénération du système nerveux*, Arch. de biol. **25**:269-388, 1910. (d) Weiss, P.: *In Vitro Experiments on Factors Determining Course of Out-Growing Nerve Fiber*, J. Exper. Zool. **68**:393-448 (Aug. 5) 1934.

18. Denny-Brown, D.: *Importance of Neural Fibroblasts in the Regeneration of Nerve*, Arch. Neurol. & Psychiat. **55**:171-215 (March) 1946.

19. His, W., cited by Ramón y Cajal.⁷

20. Held, H., cited by Ramón y Cajal.⁷

21. Heidenhain, M.: *Plasma und Zelle*, Jena, Gustav Fischer, 1911, vol. 2, p. 687.

22. Young, J. Z.: *Contraction, Turgor and the Cytoskeleton of Nerve Fibers*, Nature, London **153**:333-335 (March 18) 1944.

23. Weiss, P., and Taylor, A. C.: *Impairment of Growth and Myelinization in Regenerating Nerve Fibers Subject to Constriction*, Proc. Soc. Exper. Biol. & Med. **55**:77-80 (Jan.) 1944.

fibers are tightly bound into a compact funiculus which is ensheathed by perineurium, the strength of which is a feature of the mesodermal supporting framework of the nerve. Further evidence of a "translatory movement of axoplasm" under the influence of central forces is provided by the swelling which appears proximal to the constriction of a fiber.²³

Since the regeneration of axons is largely a manifestation of forces which proceed from the cell body, it is clear that the rate of growth will be proportionate to (1) the capacity of the cell to reform its fiber and (2) the tissues through which the axons must pass and which constitute the peripheral resistance which must be overcome by the intrinsic forces of growth.

FACTORS AFFECTING CAPACITY OF THE CELL TO REFORM THE INJURED FIBER AND RATE AT WHICH THIS IS EFFECTED

Age.—In general, the rate of growth is influenced by the age of the organism, being maximal in early life and slowly declining later. The results of Gutmann and associates^{2a} indicate that the rate of advance of axon tips down the nerve is of the same order in both young and old and that the rapid recoveries observed in young animals are more likely to be due "to great shortening of the delay in the suture scar, and probably acceleration of functional completion, combined, of course, with the fact that the distances to be covered are small." Whether or not the rate of regeneration of human nerves is more rapid in the young remains to be proved; no evidence on this point has been provided in the present series.

Chemical Agencies.—The vitality of the axon is influenced by deficiencies of vitamins and other essential factors in the body fluids and by the presence of toxins. No positive evidence is available, however, as to the extent to which regeneration of injured nerves could be affected by such factors, which did not operate in any of the present series of cases.

Temperature.—Deineka²⁴ expressed the belief that a rise in temperature increased the activity of regeneration. While the present material did not permit a study of these influences, the thermal variations between summer and winter appeared to have no effect.

Duration of the Period of Denervation.—The studies of Holmes and Young²⁵ have shown that the capacity of the central stump to throw out axon sprouts is not affected by the period of denervation. There is little information, however, relating to the rate of advance of

24. Deineka, D.: L'influence de la température ambiante sur la régénération des fibres nerveuses, *Folia neurobiol.* 2:13-24, 1908.

25. Holmes, W., and Young, J. Z.: Nerve Regeneration After Immediate and Delayed Suture, *J. Anat.* 77:63-96 (Oct.) 1942.

sprouts whose appearance has been delayed. Tables 2 and 3 contain data which demonstrate (1) that the capacity of the central stump for sprouting is retained for long periods and (2) that, after short and long periods of denervation, there may be little difference in the time taken to cover corresponding segments of the nerve (which is a measure of the rate).

It is possible that after very long delays the capacity of the cells to propel the axon distally may have waned, with a consequent reduction of the velocity of growth. Whether such a reduction, however, is to be assigned to an intrinsic factor, or solely to factors operating in the peripheral stump, remains obscure.

Level of Lesion and Length of Time for Which Nerve Has Been Regenerating.—Evidence has been obtained which suggests that the rate at which regenerating fibers advance through a given segment of a nerve is not influenced by the level at which the nerve is injured. In a series of cases, the interval between the first appearance of recovery in two muscles innervated by the injured nerve was compared with the level of the injury; an example for this purpose was provided by the intrinsic muscles of the hand, the time recorded being the interval between the appearance of recovery in the hypothenar group of muscles and its appearance in the first dorsal interosseous muscle (table 3). Whether the lesion of the ulnar nerve was high or low (considering the cases of axonotmesis and those of suture separately), this interval did not vary significantly. Thus, the level of the injury does not affect the rate in any given segment of the nerve. Furthermore, since in these cases regeneration had been proceeding for a longer period in the high lesions, these observations also indicate that the length of time for which the nerve has been growing is not a factor influencing the rate.

Distance of Growing Axon Tips from Parent Neurons.—It has been shown that there is a relationship between the progressive diminution of the rate of regeneration and the distance of the growing axon tips from their cell bodies. Thus, the initial rate is faster when the lesion is close to the parent neurons and slower when the lesion is more remote. In the former case, the rate slowly diminishes and, on reaching the more distal level, approximates the commencing rate of regeneration for a lesion in that segment. This diminution in rate could be attributed to the progressive decline, as the distance of the axon tips from the cell body increases, of the two factors on which its advance depends, namely, (a) the capacity of the cone of growth for active movement and (b) the intracellular pressure propelling it distally.

It follows from the last two considerations that, though the level of the injury does not affect the rate in any given segment of the nerve, it influences the initial velocity, which is greater with high than with low lesions. Furthermore, two factors, which greatly influence the

result, are constantly operating in any calculation of the rate: (a) the length of nerve over which the rate is calculated and (b) the levels at which the measurements are taken. These two factors must always be considered when one is comparing rates of regeneration.

FACTORS CONSTITUTING PERIPHERAL RESISTANCE WHICH INTRINSIC GROWTH FORCES MUST OVERCOME

Factors Operating at Site of Injury.—Ramón y Cajal⁷ observed that advancing axons were retarded as they traversed scar tissue. It has recently been demonstrated that localized constriction of a nerve "deprives that part of a regenerating fiber lying beyond it of some factor essential for its further growth in width and myelinization."²³ Whether or not the rate of longitudinal growth was also retarded was not determined, but there was sufficient evidence to suggest that functional maturation certainly would be delayed.

There is some evidence that growth along the peripheral stump is impeded by fibrosis of the nerve at the site of injury. Thus, the rate of regeneration following axonotmesis is greater than the rate following suture; with axonotmesis scarring at the site of injury is minimal, while with suture the scar at the site of union is more pronounced. Presumably, if the axon is forced distally under the influence of central changes, the scar tissue could, by acting as a sieve, introduce a constrictor effect on the growing fibers which would be continuously applied throughout the reconstitution of the axonal pathway and which would result in a reduction of the rate of advance of functional maturation.

In the absence of histologic examination of the injured segment of a nerve it is difficult to assess the severity of the lesion. The amount of extraneuronal injury is not a reliable guide, since minor lesions to the nerve are often associated with severe damage to tissue, and vice versa. The duration of the latent period, however, suggests a basis for comparison, the lesion being judged severe when the latent period is prolonged and mild when it is short. The important components of the latent period in this connection are (a) the initial delay and (b) the growth time; the remaining component (c), the terminal delay, depends on the duration of the other two, rising as they increase and falling as the period of denervation decreases (see later discussion).

The slower rate of advance of maturation down the distal segment following suture as compared with that following axonotmesis suggests that the severity of the lesion does affect the velocity, and there is some reason for attributing this slower rate to scar tissue at the site of union.

On the contrary, there is evidence that, within the axonotmesis and the suture group (each considered separately) the severity of the lesion may vary considerably without apparently influencing the rate.

Thus, in a number of cases of axonotmesis at approximately the same level of the ulnar nerve, though there was great disparity in the latent periods, the time taken to travel the distance between the same two muscles was approximately the same. Here, the great disparity in the latent periods could be due to variations in one of, or to a combination of, the following factors: (a) the initial delay, (b) the growth time and (c) the terminal delay.

An increase in the latent period means an increase in the terminal delay, which, in turn, signifies a proportionate increase in the time occupied by the initial delay and growth. In the cases cited, however, significant differences in the time of growth, and therefore in the rate, are unlikely, because the lesions were at about the same level, and approximately the same time was taken to travel the distance between the same two muscles, individual variations in the distances to muscles being too small to be significant. It is reasonable, therefore, to assume that the variations in the latent period involve corresponding variations in the initial delay and that these are indicative of the severity of the nerve lesion. As already pointed out, despite these variations in the initial delay, and therefore, presumably, in the severity of the lesion, the rates in the cases referred to remained substantially the same. Assuming, on the basis of the results following suture, that scar tissue is responsible for slowing the rate, it would appear that an increased initial delay after axonotmesis is not due solely to an increase in the elements obstructing the passage of the regenerating fibers; such an assumption is consistent with the appearance of the nerve at exploration and with the resultant restoration of function. The morphologic basis of the variations in the initial delay in cases of axonotmesis remains obscure, but it seems that, in some injuries at least, there are factors operating which do not affect the rate.

That variations in the initial delay do not invariably affect the rate following suture is suggested by the findings in the following case:

CASE 322.—O. A. R. sustained a gunshot wound of the upper third of the left arm on Oct. 21, 1944, which completely severed the ulnar and median nerves and the brachial artery. On Feb. 21, 1945, the median nerve was sutured under moderate tension, and the ulnar nerve, under such considerable tension that it was thought advisable to reexplore and resuture it on June 6, 1945, at which time the union was effected without tension. The nerves were sutured at about the same level. The advance of the axons was traced by following Tinel's sign distally. The sign was elicited 200 mm. below the union of the ulnar nerve one hundred and thirteen days after suture and 180 mm. below the union of the median nerve two hundred and eighteen days after suture. The difference in the distances covered could have been due to the faster growth of the ulnar axons. On the other hand, it could be attributed to the more accurate operative apposition of the stumps of the ulnar nerve, with improved conditions at the site of union, thereby resulting in a shorter initial delay; that this is the more likely explanation is supported by the observation that farther distally the calculated rates for the two nerves approximated (table 5).

Infection and Scarring: If a comparison is made of the progress of recovery in cases in which wound infection and scarring are significant, on the one hand, and the progress in cases in which these factors are absent or insignificant, on the other, it will be seen that they are inconstantly related to those factors which signify a slower rate (e. g., the time taken to travel the distance between the same two muscles). It seems that wound infection and scarring, in themselves, are not necessarily factors of importance in retarding the process of repair; their effect would appear to depend on the extent to which they add to the severity of the nerve lesion.

Conclusions: The rate of growth for corresponding sections of the nerve after suture is slower than that after axonotmesis. This seems to be due to factors operating at the site of union which appear to be associated with tissues obstructing and constricting the axons passing through them.

The duration of the initial delay following axonotmesis and suture (each considered separately), which is a guide to the severity and extent of the damage, may vary considerably without significantly affecting the ensuing rate of advance of maturation. It has been deduced that the morphologic changes which are responsible for variations in the initial delay in cases of peripheral nerve lesions are not the same as those responsible for the slower rate observed after suture as compared with that after axonotmesis. The morphologic basis of such variations remains obscure, but it seems that, in some injuries at least, the factors operating are such that the subsequent rate of advance of maturation along the distal segment, both for the initial stage and for the diminution that follows, is not significantly affected.

The progress of repair is adversely affected by wound infection and scarring only when, and so far as, these factors add to the severity of the nerve lesion.

Factors Operating in Peripheral Segment.—Holmes and Young²⁵ have shown that the total diameter of the peripheral stump shrinks during degeneration and that the neurilemmal tubes of which it is composed contract progressively if the stump remains uninnervated. The reduction of the lumen of each tube not only increases the resistance to the downgrowth of the axon which enters the tube but also delays or prevents the restoration of its diameter and myelination, on which two factors maturation greatly depends.

After axonotmesis, significant shrinkage of the neurilemmal tubes would be prevented by the early entry of regenerating axons. It should be noted that a long latent period in these cases does not necessarily signify a long period of denervation of the peripheral stump, since this period has been measured in terms of returning function (i. e., maturation) and not in terms of the growth of the axon. Perhaps

the shrinkage of the neurilemmal tubes contributes to the progressive diminution of the rate of regeneration, in that the distal segments of the distal stump, being denervated for longer periods than the proximal segments, will be narrower and so offer more resistance. Whether such a factor is responsible for a diminishing rate of growth is by no means certain; it would seem that the early entry and descent of the axon would prevent the shrinkage occurring to a degree to which it could influence the rate in the manner specified. Conditions similar to those after axonotmesis might be said to obtain after early suture. The interval between the times of functional reinnervation of the same two muscles after early suture is, however, greater than that after axonotmesis (axonotmesis and suture, ulnar group, table 3). Furthermore, in cases of late suture the conditions are different in that the neurilemmal tubes have had ample time to shrink before the entry of axons. In these circumstances, it is to be expected that the rate would be slower after late than after early suture, so that the interval between the times of functional reinnervation of the same two muscles would be much greater in cases of late suture. When cases of early and cases of late suture are compared, however, there is often no significant difference in this interval; and when there is, the longer interval is as often associated with the early as with the late suture.

There is good reason, therefore, for believing that the slower rate after suture is due not to an increase in the resistance presented by the peripheral stump but to factors related to the site of suture and probably to the scar tissue, which exerts a constrictor effect. These observations also throw doubt on the role of neurilemmal shrinkage as an agent in adversely affecting the recovery after suture.

GENERAL CONCLUSIONS

The velocity of growth is the resultant of (1) central forces provided by the cell body and (2) the peripheral resistance against which the central forces of growth act. An important peripheral factor leading to a reduction in the velocity is constriction at the site of injury due, for example, to scar tissue. This constriction may be internal or external; the relief of the latter may account for some of the rapid recoveries following neurolysis.

The progressively diminishing velocity of growth which occurs throughout the process of repair could be due to a reduction in the pressure operating from within the cell body or to a peripheral resistance which increases progressively along the peripheral stump. These observations suggest that the diminishing rate is principally the result of waning central forces of growth, which are reduced as the axon lengthens, and that the decline is not significantly contributed to by any peripheral factor in the distal stump below the site of the lesion.

Furthermore, it has been concluded that it is not the length of time for which the nerve has been regenerating which is the factor controlling the rate, but the distance of the growing axon tips from their parent cells.

Though the level of the lesion does not appear to affect the rate over any given section of the nerve, it is closely related to the initial velocity of regeneration. Thus, the rate in the initial stages of recovery is faster with high lesions, since these are close to the parent neurons, whereas when the lesion is at a lower level the initial rate is slower because the influence of the central forces of growth is weaker.

Two important factors influence a calculation of the rate: (a) the length of nerve over which the rate has been measured and (b) the level at which the measurements are taken. Both factors must always be taken into consideration when attempting a comparison of the rates of regeneration in any 2 instances.

THE LATENT PERIOD

The latent period, or interval between the date of injury and the onset of clinical recovery, comprises (a) the initial delay, (b) the period of growth and maturation and (c) the terminal delay. Differences in the latent period could be due to variations in any of these components.

Time Occupied by Growth and Maturation of Axon.—The time occupied by the growth and maturation of the regenerating fibers can be calculated from a knowledge of (a) the level of the injury with reference to a bony point, (b) the distance from this point to the structure to be innervated and (c) the rate of regeneration. In calculating the growth time in any individual specimen, there are two unpredictable sources of error: (1) individual variations in the distance to the muscles and (2) individual variations in the rate and variations imposed by the severity of the injury. In the present investigation average distances and average rates have been employed; for this reason, the calculated growth time from which the duration of the combined initial and terminal delay was derived must be regarded as approximate. Furthermore, despite the evidence that the rate following suture is slower than the rate following axonotmesis, no distinction has been drawn between the two in calculating the growth time owing to the small number of cases of suture, which renders useless any attempt to obtain a precise average rate for the different segments of each peripheral nerve. The following rates have been used in all calculations: 3 mm. per day for the upper part of the arm and the thigh; 2 and 1.5 mm. per day for the regions about the elbow and knee, respectively; 1 mm. per day for the leg and forearm, and 0.5 mm. per day for the hand and for the lower part of the leg and the foot.

When the time occupied by growth and maturation is subtracted from the latent period, the result is the combined initial and terminal delay. It is difficult to assess the relative contributions of each component in the combined delay, since there is no known clinical method of calculating the two independently, though electromyography may be developed to prove valuable for this purpose.

Initial Delay.—Immature axons cross the injured zone before the process of maturation commences. According to Ramón y Cajal's⁷ experimental observations, "one sees with certainty the axons in the peripheral stump . . . only from the 12th to the 15th day" after suture, while Perroncito²⁶ and Lewis²⁷ reported their entry after the sixth and by the fourteenth day. Gutmann and associates,²⁸ in calculating the initial delay (which they termed latent period), employed methods of extrapolation the weaknesses of which have been pointed out. They gave values of 7.27 days following plasma suture and 5.23 and 2.35 days in old and very young rabbits, respectively, after crushing.

If Tinel's sign indicates the presence of regenerating axon tips, it should provide an ideal guide to the entry of immature axons into the distal segment. Seddon and associates²⁹ obtained a negative initial delay by using this method; it appears, however, that they were misled by their assumption that the rate of growth was constant, and therefore representable on their graphs by a straight line. In only 1 case of the series which I studied (9 cases of suture and 3 in which the nerve was in continuity) was the sign observed soon after its appearance; it was elicited 15 mm. below the suture thirty-three days after union. If the rate of growth was 3 mm. per day, the initial delay would have been twenty-eight days. In the remaining cases the axons had advanced over considerable distances before the descent of Tinel's sign was recorded metrically. The calculation of the initial delay in these cases of regenerating axons involves the estimation of the time occupied by growth, for which it is necessary to take into consideration any significant decline in the rate. This is difficult, since the rate could not be calculated over the section of the nerve extending from the lesion to the first measured point where Tinel's sign was elicited (for which a knowledge of the initial delay would be necessary). To overcome this, a constant rate of 3 mm. per day was used for obtaining values for the initial delay, which must, therefore, be regarded as approximate only. The values were: (1) lesion in continuity: six, two hundred and twenty-five, and two hundred and eighty-seven days; (2) after suture: three, fifteen, twenty-one, thirty-six, forty, forty-two, forty-six, and

26. Perroncito, A.: Die Regeneration der Nerven, Beitr. z. path. Anat. u. z. allg. Path. 42:355-466, 1907.

27. Lewis, D.: Principles of Peripheral Nerve Surgery, J. A. M. A. 75:73-77 (July 10) 1920.

one hundred and fifty-eight days. Using Tinel's sign to detect the first appearance of axons in the peripheral stump, Dustin ^{8b} found that the initial delay after a good suture varied from thirty to sixty days.

There is, therefore, reliable evidence that after the suture of human nerves the entry of axon tips into the peripheral stump may be delayed for periods far exceeding those observed experimentally.

It is more difficult to assess the time required for the maturation of the axons in the central stump and injured zone. Reference has been made to the experimental efforts of Gutmann and associates ^{2a} to calculate the initial delay by extrapolation. From a study of returning sensory function following a crush injury, they obtained an initial delay of 9.76 days in one set of experiments and 19.0 days in another. A study of returning reflex motor activity gave initial delays as follows:

After crushing: 20.77 and 21.6 days in adults and 10.2 days in the very young

After suture: 32.35 and 36.5 days in adults and 16.2 days in the very young

Attention has already been directed to the unsatisfactory features of this method of calculation. Furthermore, there is no evidence that the recovery of reflex activity requires a degree of maturation comparable with that demanded for the recovery of function as studied in human material.

Seddon and associates ^{2b} also used extrapolation in their estimation of this period in clinical material. Excluding the cases in which a negative reading was obtained, extrapolation gave the following values for the radial nerve:

After axonotmesis: 25, 29, 69, 71, 103, 185 and 218 days, with average of approximately 14 weeks

After suture: 68, 80, 132, 135, 151 and 155 days, with average of approximately 17 weeks

In a later section in their paper, these authors gave "six or eight weeks for an unduly long latent period" in cases of axonotmesis of the radial nerve. This inconsistency was not explained.

Though the initial delay for matured fibers defies precise measurement, there is evidence, other than that provided by extrapolation, that it varies from one person to another. Thus, when the same nerve in 2 cases (for example cases 176 and 235, both cases of axonotmesis of the ulnar nerve with a concomitant bone injury due to a gunshot wound) has been injured at different levels, the reappearance of contraction in the same muscle (for example, the hypothenar group) may occur after about the same interval, differences appearing in the calculated combined initial and terminal delays in these cases. The following factors could be contributory:

1. Individual differences in the rate of growth and in the distance to the muscle. Despite the possibility of such variations, it is most unlikely that they would be of sufficient magnitude to account for the observed differences in the delay.

2. Variations in the terminal delay. Since the same muscle is involved (admittedly, with possibly differing intramuscular factors in different persons) and the period of denervation is substantially the same, it is reasonable to assume that any difference in the terminal delay would be so small as to be unimportant.

3. Variations in the initial delay. This would appear to be the most probable explanation of the difference in the duration of the combined delay. In a previous section relating to the effect of the severity of the lesion on the ensuing rate of regeneration, it was also deduced that the initial delay is subject to variation.

Conclusions: Analysis of the available evidence indicates that the initial delay for both axon tips and the matured fiber may vary from a few days to several months. Governing factors are the extent and density of the obstructing tissues in the injured segment of nerve, the length of the injured segment and the amount of retrograde degeneration. These morphologic features are, in general, related to the causative injury. Excluding the exceptions, the evidence suggests that these changes are minimal in minor injuries and maximal in stretch injuries and in injuries due to severe gunshot wounds with a concomitant bone injury, prolonged infection and considerable scarring. That the factors which are responsible for the duration of the initial delay are often more complicated than the morphologic changes referred to is suggested by the cases in which a prolonged initial delay is not associated with any alteration in the rate, with any permanent defect of function or with any change in the nerve which could be detected at operation by inspection and palpation.

Terminal Delay.—The terminal delay comprises the time required for (1) regeneration in the muscle from the surface to the end organ and (2) recovery of capacity for effective contraction of reinnervated muscle fibers.

Gutmann and Young²⁸ demonstrated in the rabbit that after a crush injury close to the muscle, "fibers arrive back near the end-plates about 12 days after the operation, whereas electrical stimulation of the nerve produced contraction first on the 18th day and reflex functioning appeared on the 23rd day." They stated that the corresponding times after suture were greater and that these steadily increased with increasing periods of denervation.

28. Gutmann, E., and Young, J. Z.: The Re-Innervation of Muscle After Various Periods of Atrophy, *J. Anat.* **78**:15-43 (Jan.) 1944.

No precise data relating to these events are available in man. Though motor fibers run complicated, and often long, courses within the muscle before reaching their final destination, the distance to be covered before functional recovery follows is not known. The rate at which functional regeneration proceeds within the muscle is also not known; it probably does not differ greatly from that just external to the muscle. Thus, in muscle innervated in the vicinity of the elbow and knee rates of approximately 2 and 1.5 mm. per day, respectively, may be expected; in the midforearm and leg, a rate of 1 mm. per day, and in the hand and foot, a rate of 0.5 mm. per day. In arriving at these estimates, it should be noted that the rate falls to a minimum as the length of the fiber increases and not necessarily as the terminal part of the fiber is being reconstituted; thus, the terminal portion of a very long fiber would be reconstituted at a very slow rate, while the corresponding portion of a short fiber would be laid down at a more rapid rate.

Another factor influencing the terminal delay in human material is the latent period, or duration of the period of denervation. In this connection, a study of the combined initial and terminal delay following axonotmesis for each of two muscles innervated at different levels along the same nerve has proved instructive. Since the initial delay in such cases is the same for each muscle, any significant difference in the combined delay could be attributed to an increase in the terminal delay occurring in the more distal muscle. Thus, in case 31 (injury of the ulnar nerve) the two muscles selected were the flexor carpi ulnaris and the hypothenar group. For each muscle, the distance from the lesion to the muscle, the rate employed in calculating the growth time, the period of denervation, the growth time and the calculated combined delay were tabulated.

Flexor carpi ulnaris:	133 mm.	2 mm.	27 wk.	10 wk.	17 wk.
Hypothenar group:	412 mm.	2 mm. for the first, 133 mm. and 1.0 mm. thereafter	80 wk.	50 wk.	30 wk.

Since the initial delay is the same, the greater combined delay in the case of the muscles of the hypothenar group could be attributed to the following factors:

1. An error in the growth time, owing to a greater decline in the rate of advance than that allowed for. The rate for the first 133 mm. would be the same as that for the fibers destined for both muscles, namely, 2 mm. per day (see criteria for selection of clinical material and its use in calculating rates of regeneration); even if the rate distal to this level were reduced to a figure just above that obtaining for the section of the nerve in the hand, the disparity in the combined delay would still be considerable.

2. Individual variations in the distances to the two muscles. These are too small to account for the magnitude of the difference in the combined initial and terminal delays.

3. An increase in the terminal delay. This is the most probable explanation, though the length of the delay will depend on the value assigned to (a) the growth rate and (b) the distances to the muscles.

Such an analysis of the data contained in tables 2, 3, 4 and 6 indicates that in human material the terminal delay rises with the period of denervation (latent period).

Finally, reference has been made in an earlier section to the electromyographic¹¹ studies, which indicate the entry of fibers into muscles prior to their recovery of voluntary contraction and, also, to the recovery of the excitability of the motor unit to direct stimulation of the nerve before the reappearance of voluntary contraction. To what extent the delay between the two phases of recovery is attributable to an intramuscular factor is not revealed by such studies.

These generalizations, while indicating the significance of the terminal delay as a contributing factor to the combined delay, do not permit a metrical expression of its value. The delay will be influenced by such factors as (a) the intramuscular distance to be traveled by the regenerating fibers and the rate at which they advance within the muscle; (b) the period of denervation [this depends on (1) the level of the injury, (2) the rate of regeneration of the axons and (3) the initial delay], and (c) the degree and pattern of reinnervation.

COMBINED INITIAL AND TERMINAL DELAY

For reasons emerging from the foregoing discussion, it has been considered preferable not to attempt any separation of the initial and terminal delays when analyzing the latent period, but to regard the two as comprising a combined period of delay in the process of repair. The same policy was adopted in a previous reference to this interval following lesions of the radial nerve, but in that study the term "initial delay" was employed to cover both the initial and the terminal delay.¹² It is now felt, however, that the use of this term to cover both components is confusing and that it would be preferable, therefore, to introduce the term "combined initial and terminal delay." In calculating the values for this period, which are given in table 6, cases were selected in which the lesions were relatively close to the first muscle innervated below the lesion. This was done for the following reasons.

(a) To minimize errors in the growth time which would be introduced over very long distances by an individual variation in the rate. Thus, over a distance of 300 mm. a rate of 1.5 mm. per day, as opposed to one of 1.0 mm. per day, would mean a difference of one hundred days in the growth time: over a distance of 90 mm. the difference would be thirty days.

TABLE 6.—Data Employed in Estimating Relative Contributions to Latent Period of Growth Time and of Initial and Terminal Delays.

Causative Injury; Nature of Nerve Lesion; Case No.	Level of Lesion, Mm.*	First Muscle to Recover †	Distance from Lesion to First Muscle to Recover, Mm.	Rate, per Day, Min.	Latent Period	Combined Initial and Terminal Delay
Radial nerve						
(a) Axonotmesis						
Simple fracture of the humerus						
Case 77.....	100 above L. H. E.	BR.	82	2.0	16	10
161.....	100 above L. H. E.	BR.	82	2.0	13	7
317.....	100 above L. H. E.	BR.	82	2.0	16	10
Gunshot wound						
Case 185.....	120 above L. H. E.	BR.	102	2.0	14	7
203.....	90 above L. H. E.	BR.	72	2.0	20	15
255.....	20 above L. H. E.	BR.	2	2.0	8	8
264.....	10 above L. H. E.	E. C. R. L.	15	2.0	14	13
Gunshot wound + fracture of humerus						
Case 100.....	75 above L. H. E.	E. C. R. L.	80	2.0	23	17
106.....	50 above L. H. E.	BR.	32	2.0	17	15
118.....	90 above L. H. E.	BR.	72	2.0	16	11
231.....	125 above L. H. E.	BR.	107	2.0	40	32
258.....	50 above L. H. E.	BR.	32	2.0	18	16
(b) Suture						
Laceration						
Case 180.....	40 above L. H. E.	E. C. R. L.	45	2.0	20	17
282.....	125 above L. H. E.	BR.	107	2.0	22	14
Gunshot wound						
Case 40.....	50 above L. H. E.	E. C. R. L.	55	2.0	20	16
Ulnar nerve						
(a) Axonotmesis						
Laceration						
Case 103.....	50 above R. S. L.	H.	82	1.0	20	8
323.....	20 below R. S. L.	H.	12	1.0	8	6
Gunshot wound						
Case 31.....	100 above M. H. E.	F. C. U.	133	2.0	27	17
237.....	80 above R. S. L.	H.	112	1.0	34	18
Gunshot wound + bone injury						
Case 235.....	10 above R. S. L.	H.	42	1.0	29	23
(b) Suture						
Laceration						
Case 139.....	10 above R. S. L.	H.	42	1.0	28	22
158.....	25 above M. H. E.	F. C. U.	58	2.0	18	14
290.....	At M. H. E.	F. C. U.	33	2.0	17	15
325.....	80 above R. S. L.	H.	112	1.0	40	24
Gunshot wound						
Case 38.....	80 above R. S. L.	H.	112	1.0	17	1
183.....	70 above M. H. E.	F. C. U.	103	2.0	28	21
207.....	60 above M. H. E.	F. C. U.	93	2.0	14	7
Gunshot wound + bone injury						
Case 100.....	60 above M. H. E.	F. C. U.	93	2.0	30	23
Sciatic nerve						
(a) Axonotmesis						
Compression						
Case 188.....	Neck of fibula	P. L.	19	1.5	21	19
		T. A.	28	1.5	21	18
245 (right leg)	Neck of fibula	P. L.	19	1.5	20	18
245 (left leg)	Neck of fibula	P. L.	19	1.5	18	16
		T. A.	28	1.5	18	15
Simple fracture of femur						
Case 326.....	100 above M. F. E.	G.	131	1.5	29	17
Gunshot wound						
Case 82.....	Head of fibula	P. L.	19	1.5	18	16
		T. A.	28	1.5	18	15
95.....	50 above M. F. E.	G.	81	1.5	15	7
		P. L.	144	1.5	19	5
109.....	70 above M. F. E.	G.	101	2.0	13	6
190.....	At M. F. E.	G.	31	1.5	22	19
		P. L.	19	1.5	7	5
254.....	Head of fibula	T. A.	28	1.5	7	4
Gunshot wound + bone injury						
Case 260.....	50 above M. F. E.	G.	81	1.5	12	4

* L. H. E. indicates the lateral epicondyle of the humerus; R. S. L. and M. H. E., the level of the styloid process of the radius and the medial epicondyle of the humerus, respectively, and M. F. E. the medial epicondyle of the femur.

† BR. denotes brachioradialis; E. C. R. L., extensor carpi radialis longus; H., hypothenar muscles; F. C. U., flexor carpi ulnaris; P. L., peroneus longus; T. A., tibialis anterior; G., gastrocnemius.

(b) To minimize errors due to the declining rate, which would increase with the length of the nerve.

(c) To shorten the period of denervation, which would reduce the duration of the terminal delay.

The combined delay varied from one to thirty-two weeks, with a mean of thirteen weeks following axonotmesis and sixteen weeks following suture.

Influence of Infection and Scarring.—It is difficult to assess the effect of wound infection and scarring on the duration of the latent period, since there were cases in which despite their absence the latent period was prolonged, whereas there were other cases in which severe infection and scarring were associated with a very short latent period. The principal factor affecting the duration of the latent period is the severity of the nerve lesion. The effect of infection and scarring will, therefore, depend on the extent to which they add to the severity of the nerve lesion. For this reason their influence is variable. It may be concluded that while wound infection and scarring may increase the hazards of repair and the duration of the latent period, there is reliable evidence that they may be severe without retarding the progress of recovery.

Conclusions.—The combined initial and terminal delay varied from one to thirty-two weeks, with a mean of thirteen weeks, following axonotmesis and sixteen weeks after suture. It rose as the distance of the lesion from the muscle increased; this was due to an increase in the terminal delay consequent on an increase in the period of denervation.

The combined delay was of longer duration in the cases of severer lesions. This is attributed to the following factors:

1. An increased initial delay, which, in turn, may be due to an increase in the amount, extent and density of obstructing tissues in the injured segment or to factors which do not result in the same gross pathologic change.

2. An increase in the terminal delay occasioned by an increase in the period of denervation. The increase in the period of denervation is due to the increased initial delay and to the slower rate of growth of axons when this is associated with it.

SUMMARY

A. Methods previously employed to calculate the rate of regeneration are reviewed in detail, with especial reference to those used to study this process in human peripheral nerve injuries.

B. From a study of the rate of regeneration in a series of human peripheral nerve injuries, the following conclusions are made:

1. There are two separate events in the process of repair: (a) regeneration of the axon, and (b) functional maturation of the axonal pathway, which involves further morphologic changes of a complex character, such as myelination and the restoration of fiber diameter. The second process proceeds at a slower rate than does the advance of the axon.

2. The velocity of regeneration for both processes diminishes progressively over the whole period of recovery.

3. There is a relationship between the progressive diminution of the rate of regeneration and the distance of the growing axon tips from their cell bodies. Thus, the initial rate is faster when the lesion is close to the parent neurons and slower when the lesion is more remote. In the former case, the rate slowly diminishes and, on reaching the more distal level, approximates the beginning rate of regeneration for a lesion in that segment.

4. After axonotmesis, the rate of advance of functional maturation over the proximal portion of the nerve (arm and thigh) is in the vicinity of 3 mm. per day and slowly diminishes to approximately 0.5 mm. per day over the distal portion (hand and foot). The rate following suture is slower for all sections of the nerve—it was, however, not possible to ascertain precisely to what extent this was so.

5. After suture, the axon tips advance down the forearm and leg at a rate, in the vicinity of the elbow and knee, of approximately 3 and 2 mm. per day, respectively, but this rate gradually slows until at the wrist and ankle it is commensurate with that observed for functional completion.

C. The factors responsible for individual variations in the rate and for its progressive decline throughout the process of repair are discussed in detail.

1. The velocity of regeneration is the resultant of (a) central forces provided by the cell body and (b) the peripheral resistance against which the central growth forces act.

2. The observations suggest that the diminishing rate is principally the result of waning central forces of growth, which are reduced as the axon lengthens, and that the decline is not significantly contributed to by any peripheral factor in the distal stump below the site of the lesion. Furthermore, it is not the length of time for which the nerve has been growing which is the factor controlling the rate but the distance of the growing axon tips from the parent cells.

3. An important peripheral factor leading to a reduction in the velocity is constriction at the site of injury, due, for example, to scar tissue, which may be situated within or around the nerve.

4. The level of the lesion does not appear to affect the rate over any given section of the nerve but is closely related to the initial velocity of regeneration. Thus, the rate in the initial stages of recovery is faster with high lesions, since these are close to the parent neurons, whereas when the lesion is at a lower level the initial rate is slower because the influence of the central forces of growth is weaker.

5. Two factors must always be taken into consideration when attempting a comparison of the rate of regeneration in any 2 instances: (a) the length of nerve over which the rate is calculated, and (b) the levels at which the measurements are taken.

D. The latent period, or interval between the date of injury and the onset of clinical recovery, is analyzed. It comprises (a) the initial delay, (b) the time occupied by the growth and maturation of the regenerating axons and (c) the terminal delay. All three components are defined and discussed.

1. Information required for the calculation, in any case, of the time occupied by the growth and maturation of the regenerating axon is provided.

2. For reasons fully set out, it is considered preferable not to attempt any separation of the initial and the terminal delay when analyzing the latent period, but to regard the two as comprising a combined period of delay in the process of repair.

(a) The combined delay varied from one to thirty-two weeks, with a mean of thirteen weeks after axonotmesis and of sixteen weeks after suture.

(b) The combined delay rose as the distance of the lesion from the muscle increased; this was due to an increase in the period of denervation.

(c) The combined delay was of longer duration with the severer lesions. This is attributed to two factors: (1) an increased initial delay, which, in turn, is probably due to an increase in the amount, extent and density of obstructing tissues in the injured segment. These morphologic features are in general related to the causative injury. Excluding the exceptions, the evidence suggests that these morphologic changes are minimal with minor injuries and maximal with stretch injuries and injuries due to severe gunshot wounds with concomitant bone injury, prolonged infection and considerable scarring. (2) An increase in the terminal delay occasioned by the increase in the period of denervation, which is due to the increased initial delay and to the slower rate of growth of axons when this is associated with it.

E. It is concluded that repair is adversely affected by wound infection and scarring only when, and so far as, these factors add to the severity of the nerve lesion.

A RATIONAL SUBDIVISION OF THE CEREBRAL CORTEX

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THE STUDY of regional peculiarities of the structure of the cerebral cortex as revealed by certain features and the division of the cortex into structural units on the basis of these features constitute the main problem of the architectonics of the cerebral cortex. These features are of varying value. Some of them are of major importance and should form the basis for division of the cerebral cortex into main territories. Others are of more specific significance and serve to subdivide the main territories into regions, subregions, areas and subareas, according to a certain hierachial order and depending on their relative importance. Finally, there is an enormous number of less important features, allowing subdivision of the cortex literally *ad infinitum*. As a matter of fact, no part of the cortex, however small it may be, exhibits absolute similarity to the neighboring part.

It would be possible to consider these structural modifications as special areas and subareas—all depends on one's understanding of the concept "area," which so far has no generally recognized definition. However, as I have already emphasized in one of my previous papers:

Von wesentlicher Bedeutung ist aber der Umstand, dass bei einer solchen allzu weitgehenden Differenzierung das Prinzip der Felderung selbst seinen Wert zu verlieren beginnt. Darum müssen hier gewisse Grenzen gesetzt werden, und die Arbeit muss nicht nur in der Richtung der Differenzierung, sondern auch in der Richtung der Integrierung vor sich gehen, d. h. der Vereinigung der kleiner Formationen, die sich voneinander nur durch unwesentliche Merkmale unterscheiden, in Formationen höherer Ordnung, deren Absonderung als Grund eine genügende Anzahl wesentlicher Merkmale wird (page 23).¹

"It is of essential significance that with too far reaching a differentiation the principle of division of the cerebral cortex into areas may lose its value. Certain limits are required, and work must be carried out in the direction not only of differentiation but also of integration, i.e., the unification of small formations, which are to be distinguished from one another only by unessential characteristics, into formations of a higher order, the separation of which may be justified by a sufficient number of essential characteristics."

But how can one judge whether these features are essential or not? Of course, their character as revealed by the architectonics of the adult brain is of great value in this respect, but it is the dynamics of the

1. Filimonoff, I. N.: Ueber die Variabilität der Grosshirnrindenstruktur: Regio occipitalis beim erwachsenen Menschen, J. f. Psychol. u. Neurol. **44**:1-96 (Jan.) 1932.

development of architectonic formations which is of major significance. It is quite obvious that the earlier certain features appear in the process of development, the greater should be their importance for the division of the cortex into its main regions. It is significant in this respect that division of the cortex into two chief regions—the homogenetic and the heterogenetic cortex—a classification which represents the main principle of modern cytoarchitectonics, was founded by Brodmann on ontogenetic data. The well known classification of cortical structures by Rose is also based on the ontogenetic principle.

The classification which my colleagues and I have formulated² is likewise founded on the principle of ontogenetic development. Like the Rose classification, it is based on the study not only of late stages of ontogenesis, as in Brodmann's scheme, but also of early ones and takes into consideration both the development of the cortical plate and that of the entire wall of the end brain. Like the Rose classification, it leads to division of the cerebral cortex not into two, as in Brodmann's scheme, but into three, main territories. However, our classification is based on quite another concept than that of Rose, which, in our opinion, is particularly erroneous with respect to his "schizocortex." Rose considers this portion of the cortex in contrast to his "holocortex" and presented it in his scheme as a unit, including such actually heterogenous structures as the isocortex and Ammon's cortex. Our investigations would show that the relations are just the reverse: The schizocortex ("periarchicortex" in our terminology) occupies a place intermediate between Ammon's cortex (archicortex) and the isocortex, since Ammon's plate can by no means be considered as a homologue of the isocortical plate. Our understanding of the semicortex (cortex *semi-separatus*, not cortex *semiparietinus* in the sense of Rose) is also entirely different. The cortex *bigenitus* occupies an intermediate place between the isocortex and the allocortex both in our classification (perisemical zone) and in the Rose system (between the cortex *totoparietinus* and the cortex *semiparietinus*). However, we understand this intermediate position in a quite different sense, since our concept of the genetic character of the claustrum is quite a different one.

Hence, important peculiarities of structure are concerned in the difference between the two classifications, and, of course, many specific points of distinction as well, especially with respect to stratification of the entorhinal and, in part, of the presubicular region.

The main territories of the cerebral cortex are designated in our scheme as cortex *completus* or isocortex (after O. Vogt); cortex *incompletus*, or allocortex (after O. Vogt), but with considerable limitations (*allocortex sensu strictiori*), and cortex *intermedius*, or periallocortex.

2. Sarkisov, S. A., and Filimonoff, I. N.: *Les travaux de l'Institut du cerveau*, Moscow, Izdanie Gosudarstvennogo Institute Mozga, 1938, vols. III-IV.

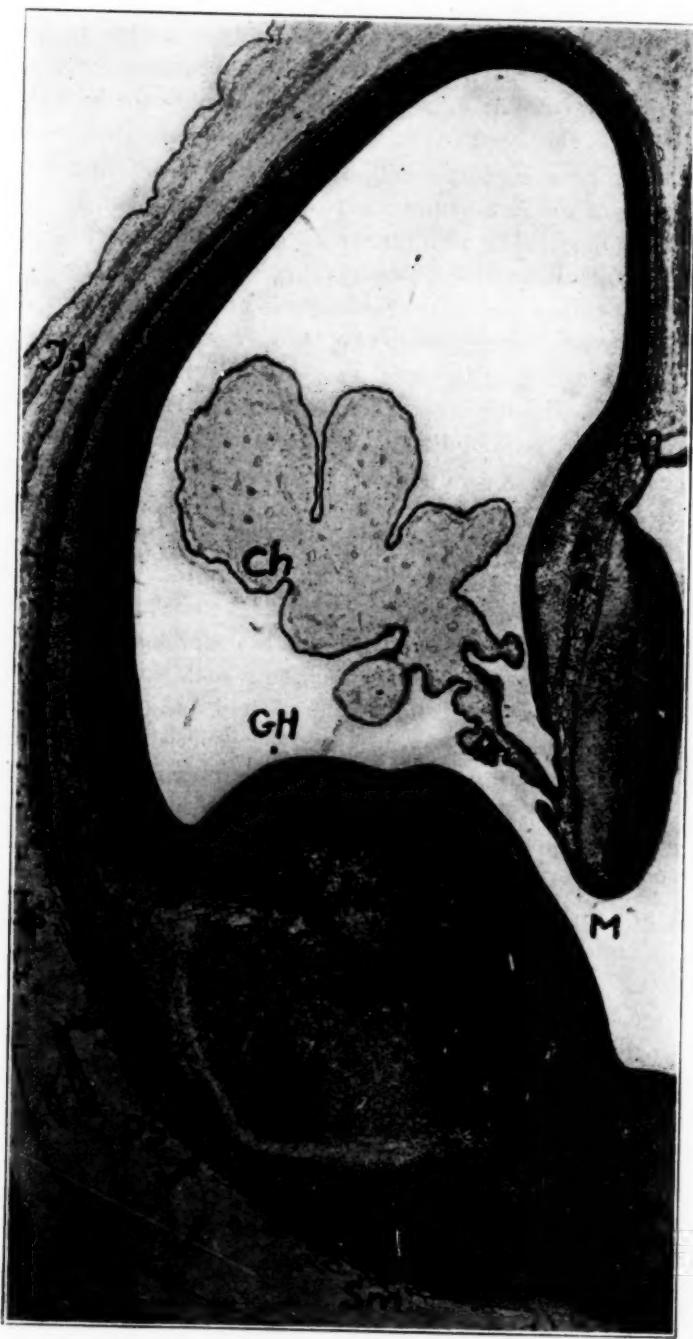


Fig. 1.—Stage, 35 mm. *A* is archicortex; *Caud*, caudate nucleus; *Ch*, choroid plexus; *Gh*, Hügel's ganglion; *Is*, isocortex; *M*, foramen of Monro; *PA*, perarchicortex; *PS*, perisemicortex; *Put*, putamen, and *Sm*, semicortex.

The cortex completus, or isocortex, includes the whole territory within which the end brain wall is characterized, even in relatively early stages of development (27 mm. stage in our material), by the presence of all the fundamental layers of His, including the clearly differentiated cortical plate (fig. 1). On the contrary, the cortex incompletus, or allocortex *sensu strictiori*, shows incompleteness of the structure of the wall in the early stages, this incompleteness being maintained to a certain extent in subsequent stages of development, including the definitive stage. The third main territory—the cortex intermedium, or periallocortex, separates everywhere the cortex completus from the cortex incompletus and is characterized by a special type of transitional structure.

The cortex incompletus, or allocortex *sensu strictiori*, includes, first, the semicortex, or semicortical zone, to which belong the tuberculum of lactorium (*T*), the diagonal region (*D*), the septum pellucidum (*Spt*), the periamyg达尔 region (*Pm*) and the prepiriform region (*Pp*), but the latter only partly, since, as a matter of fact, it presents a transition from the semicortex *sensu proprio* to a cortex of higher type, namely, the cortex intermedium (perisemicortex; see later section). The second main territory of the allocortex is represented by the archicortex, or the archicortical, or Ammon's zone, which includes the subiculum (*Sub*), the cornu ammonis (*Ca*), the fascia dentata (*FD*) and the tenia tecta (*indusium corporis callosi*).

The incompleteness of the semicortical zone is manifested by non-separation (early stages of development), or by incomplete separation, of the cortical plate from the periventricular cell masses (cortex semi-separatus). The semicortical zone is genetically connected with the condensed external sublayer of the stratum intermedium (*Z*), termed by us *Z*¹, and not with the cortical plate of the isocortex. In early stages of development (27 to 35 mm., fig. 1) it is clearly seen that the dense sublayer *Z*¹, distinctly differing from stratum *Z* proprium in its scarcity of cells and disappearing into the latter at the level of the isocortex (*Is*), comes into immediate contact with the stratum marginale (*Randschleier* of His) at the level of the semicortex (*Sm*). Thus, the semicortex generally fails to exhibit a true cortical plate homologous with the cortical plate of the isocortex.

Incompleteness of the archicortex, or Ammon's zone, is also manifested in early stages of development and is subsequently maintained, though in a modified form. In early stages of development (27 to 35 mm.) the entire brain wall within the archicortical zone (fig. 1, *A*) exhibits extreme scarcity of cellular elements; the matrix is narrow, and the complete absence of a cortical plate is an outstanding feature. At the 55 mm. stage the cortical plate appears in the archicortex also, but it differs strongly from the isocortical plate in its rarefied character and in its relatively slight separation from the subjacent stratum inter-

medium. Hence the cortical plate of the archicortex is characterized, first, by a scarcity of cellular elements and, second, by its being formed, in contrast to the isocortex, by the secondary migratory wave of neuroblasts only, the latter feature being of no less importance. With respect to time of formation, it corresponds only to the deeper layer of the cortex intermedium (see later section). The fact that Ammon's plate corresponds not to the entire cortical plate of the cortex intermedium but only to its deeper layer is still more apparent during further development in the superlamination on Ammon's plate of the isocortical plate within the cortex intermedium (see later section; compare with figures 2 and 3).

The cortex completus and the cortex incompletus differ strongly during the process of development as well as in the adult stage, as has already been mentioned; they present no immediate contiguity and are separated from each other by intermediate structures, which can be referred neither to the cortex completus nor, even less, to the cortex incompletus, and which for this reason we regard as the third main territory, the cortex intermedium, or periallocortex. The cortex intermedium, separating thus the semicortical and archicortical zones (forming together the cortex incompletus) from the cortex completus, is divided, like the cortex incompletus, into two zones—the perisemicortical and the periarchicortical zone.

The whole cerebral cortex is thus divided into three main territories, or into five main zones: the cortex completus, or isocortex; the cortex incompletus, or allocortex *sensu strictiori*, including the semicortical and the archicortical zone, and the cortex intermedium, or periallocortex, including the perisemicortical and the periarchicortical zone.

The perisemicortical zone includes the intermediate insular formations and partly also the prepiriform region, which can thus be referred to the semicortex in a rather conventional sense.

The periarchicortical zone includes the presubicular and the entorhinal region.

The presubicular region (*Psb*) bears a strong transitional character even in very early stages of embryonic development (27 to 35 mm.), when it cannot yet be separated from the entorhinal region. In this still undifferentiated stage the cortical plate is already outlined, though weakly, into regions; the periarchicortical zone, in contradistinction to the archicortex, presents a larger number of cells (fig. 1, *PA*).

At the 55 mm. stage the presubicular region is characterized by an already well formed cortical plate, which, however, is strongly narrowed as compared with the isocortex. At this stage of development it seems to present the homologue only of the upper portion of the definitive presubicular region (*Psb*), while the lower portion of the latter is formed only later by further condensation of the stratum intermedium of the wall of the brains. At the 80 mm. stage a well defined superlamination of the isocortical plate on Ammon's plate is seen in the region of the

presubiculum superius (fig. 2, *PA*), each plate presenting a wedge-shaped narrowing. Hence the upper portion of the presubiculum superius forms the continuation of the isocortical plate, and the lower portion, the continuation of Ammon's plate; the two plates are separated from each other by a clearly defined, light intermediate layer, or *stratum dissecans* (*Diss*²). The splitting in presubiculum inferius occurs at the 130 mm. stage or somewhat earlier; at the 80 mm. stage the cortical

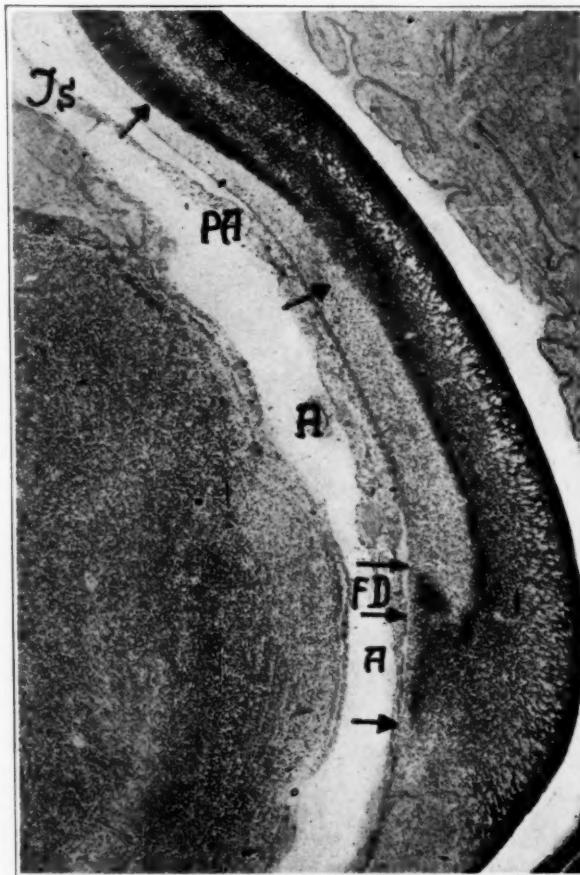


Fig. 2.—Stage, 80 mm. *A* is archicortex (subiculum and cornu ammonis); *FD*, fascia dentata; *Is*, isocortex, and *PA*, periarchicortex (here, presubiculum superius).

plate of the presubiculum inferius, which is very wide, but rarefied in its deeper part, exhibits an immediate transition *in toto* into Ammon's plate. In later stages the inner part seems to show rarefaction and merging with Ammon's plate, whereas the outer part exhibits condensation and separation from the inner part through formation of a *stratum dissecans*.

Thus, the process of splitting in the region of the presubiculum arises only secondarily and presents the result of comparatively late ontogenetic development. It is to be strongly emphasized, however, that the process of splitting follows here a quite definite direction, separating cortical plates which differ profoundly from each other, according to their genetic character.

The presubiculum region is situated in the immediate neighborhood of the archicortical zone and surrounds it almost completely. It is, accordingly, represented not only by the temporal but also by the retrosplenial, supracallosal and subgenual parts. However, its typical

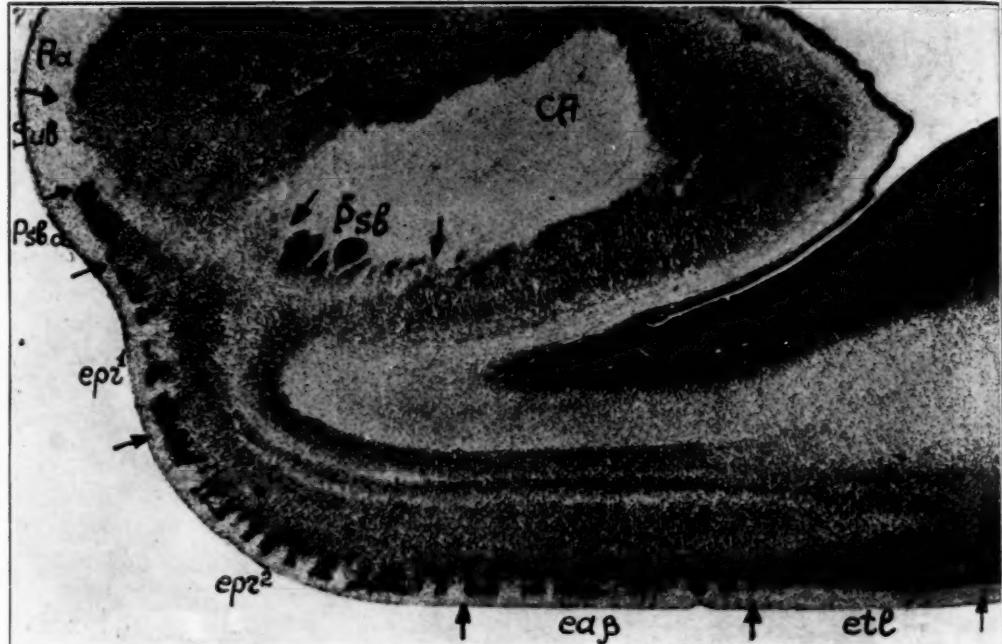


Fig. 3.—Stage, 180 mm. *Aa + CA* indicate cornus ammonis; *epr¹* (only *Diss²*) and *epr²* (*Diss¹* + *Diss²*), subregio entorhinalis propria; *ea^β* (only *Diss¹*) is subregio entorhinalis anterior; *etl*, subregio entorhinalis transgrediens lateralis; *Psba*, presubiculum anterius; *Sub*, subiculum.

structure is maintained throughout the process of development only in the temporal part. Here the upper portion (external [*ext*] and intermediate [*m*] layers) presents a granular character even in the adult, and the region maintains a typical subdivision into two structures, *Psb 1* and *Psb 2*, which show fusion into a single formation, *Psb a*, only in their oral part (fig. 3, *Psb a*). The retrosplenial part exhibits at late stages and in the adult brain four clearly differentiated formations: *Psb 1*, *Psb 1a*, *Psb 2a* and *RS*. Of these formations, only *Psb 1* has a typical presubiculum structure (granular upper portion); other forma-

tions show pyramidization either of the superficial part of the upper portion (*Psb 1a* and *Psb 2a*) or of the entire upper portion (*RS*). However, here also one must admit the presence of true presubiculum formations, as evidenced by the course of their evolution: In early stages the upper portion of the calcarine trunk is occupied in its oral part by typical presubiculum formations and in late stages, as well as in the adult, by formations *Psb 2a* and *RS*.

In the supracallosal and subgenual parts the structure of the presubiculum region is strongly modified: Its upper portion shows complete pyramidization, and in the oral part the subdivision into formations *Psb 1* and *Psb 2* becomes effaced, the region presenting even in early stages a single formation—*Psb sa*. Nevertheless, even the subgenual part of the presubiculum region, the characteristic structure of this region, remains for the most part clearly pronounced; the cortical plate of the archicortex, exhibiting large cells (here of the *tenia tecta*), penetrates into the deeper portion and on it is superimposed the external plate of the presubiculum, which presents a quite different, though nongranular structure.

The entorhinal region already shows splitting of the cortical plate at the 55 mm. stage, e. g., earlier than does the presubiculum region (*Psb*). The stratum dissecans appears here first in the deeper part of the cortical plate; during further development (fig. 4, *ep*) it becomes more superficially situated (*Diss¹*), owing to increase in the width of the cortex through apposition (from below). The deep stratum dissecans, corresponding to the stratum dissecans of the presubiculum (*Diss²*), appears in the entorhinal region only later, and not throughout the whole region. The great significance of the difference between the two strata dissecantia is to be strongly emphasized. In the presubiculum, as well as in the entorhinal, region the cortical plate is subdivided into three chief layers: external (*ext*), intermediate (*m*) and internal (*int*), only the internal one showing transition into Ammon's plate. The stratum dissecans of the presubiculum (*Diss²*) separates Ammon's plate from the upper layers (external and intermediate) of the periarchicortical zone, which correspond to the isocortical plate and overlie Ammon's plate, while the deep stratum dissecans (*Diss¹*), in a well defined form encountered only in the entorhinal region, is situated within the layer *m*. The difference between the strata dissecantia in respect to their level is clearly seen in figure 4 (at the 150 mm. stage) (*Psb 2i* and *ep*), and is also evident in formations in which the strata dissecantia are both present. (fig. 3, *epr²*).

In addition to these chief strata dissecantia, the stratum dissecans externum (*Diss ext*) is seen in some entorhinal formations, either subdividing the external layer (*ext*) into two sublayers or separating the external layer (*ext*) from the intermediate layer (*m*). A quite typical sublayer (stratum interlaminare), formed of large cells, is situated

between the two chief strata dissecentia, *Diss*¹ and *Diss*² (fig. 3, *epr*²). This sublayer is also clearly seen in many formations in which only one stratum dissecan is present (fig. 3, *eaβ*). In such cases it acquires considerable importance for adequate qualification of this stratum dissecan: The stratum dissecan situated over the stratum interlaminare

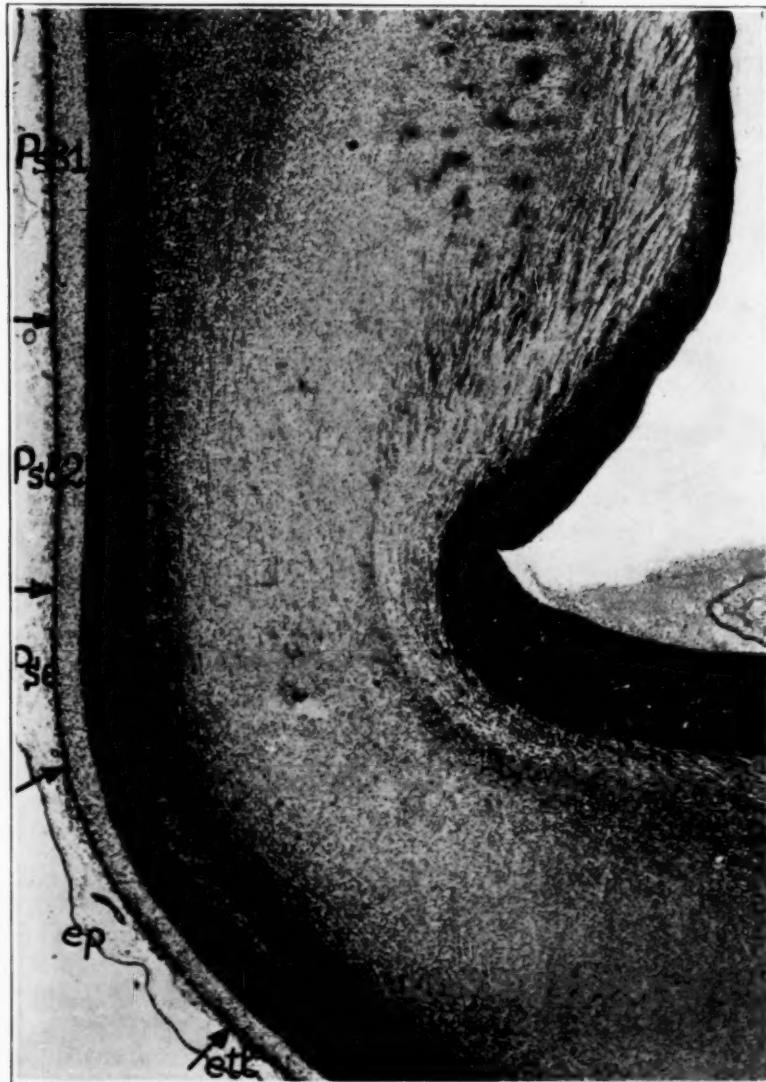


Fig. 4.—Stage, 150 mm. Here *ep* is subregio entorhinalis posterior (only *Diss*¹); *Psb* 1 and *Psb* 2 indicate regio presubicularis (*Psb* 2, only *Diss*²); *Pse*, parasubiculum.

is to be considered as stratum *Diss*¹, and the stratum dissecan, situated under this layer, as stratum *Diss*².

The complete (the ideal, so to speak) stratification of the entorhinal region can be formulated as follows: *ext* (subdivided into sublayers by

stratum *Diss ext*); *m* (+ stratum *Diss*¹ + stratum *interlaminare*); stratum *Diss*²; internal layer (*int*).

In reality, stratification in various entorhinal formations presents deviations of one sort or another from this ideal type, owing to which the entorhinal region may be subdivided at relatively early stages of development into six subregions on the basis of quite definite peculiarities. It is anteriorly, posteriorly and laterally separated from the isocortex by intermediate subregions: anterior (*eta*), posterior (*etp*) and lateral (*etl*). The chief part of the region consists of three main subregions: the posterior (*ep*), the middle, or regiopropria or media (*tpr*), and the anterior (*ea*). The entorhinal region is separated from the presubiculum region by the parasubiculum formation (fig. 4, *Pse*) and from the periamygdalar region by the formation *epm*, characterized by the disappearance of the stratum *interlaminare* (*int*) and the maintenance of the typical *ext Diss ext m* formation.

The subregion *etp* differs in early stages from the isocortex by some rarefaction in sublayer *m*, and in late stages by discontinuation of sublayer *ext* and by the absence of layer IV. At the same time, it cannot be referred to the quite typical entorhinal region, owing to the absence of the strata *dissecantia*.

The subregion *ep* is entirely typical at all stages because of the presence of a well defined deep stratum *dissecans*, *Diss*¹ (fig. 4, *ep*).

The subregion *epr* is characterized in early stages by the presence of the so-called *limes duplex* in the site of transition to the isocortex (fig. 3, *eaβ* and *etl*), and by the presence of stratum *Diss*² in the late stages (from 180 mm. to the adult), the latter being absent in all other entorhinal subregions. Only stratum *Diss*² is present in the formation *epr*¹ and both stratum *Diss*¹ and stratum *Diss*² are seen in formation *epr*² (fig. 3, *epr*¹ and *epr*²). In early stages (130 to 150 mm.) the formation *epr*¹ is characterized by the absence of true strata *dissecantia*; only rarefaction of the *m* layer (*pseudodissecans*) is to be seen, while in the formation *epr*² only stratum *Diss*¹ is clearly defined.

Subregion *ea* is characterized by the presence of stratum *Diss*¹ alone (fig. 3, *eaβ*) and is relatively early subdivided into two quite distinct parts: internal (*ea*¹) and external (*ea*). At later stages, each of these parts is differentiated into separate formations according to more special features: *ea* into *eaα*, *eaβ* and *eaγ*; and *ea*¹ into *ea*^{1α}, *ea*^{1β}, *ea*^{1γ} and *ea*^{1δ}.

The anterior intermediate subregion, *eta*, is subdivided into formations *eta*¹ and *eta*²; between these formations and the prepiriform region is situated the *ρ per* formation, where the layer *ext* presents a quite typical aspect for the region *Pp*, but where the cortical plate, at the same time, shows the presence of stratum *Diss*¹ and the internal layer (*int*). The intermediate formation *eti* forms a transition of the subregion *eta* into the insular (perisemantic) region.

The intermediate formations in this region (*epr*⁰ and *epr*^{oo}, between the subregions *ep* and *epr*; the aforementioned formations *Pse* and *epm*, and so forth), as well as in other regions, are numerous.

One general principle prevails throughout the entire process of ontogenesis, which I shall designate as the principle of intermediate formations: Between formations showing strong structural or, especially, genetic differences, one is sure to detect intermediate formations, the structure of which bears to a certain degree a transitional character, these formations being, however, sharply (*saarscharf*) separated from each other. This principle forms also the basis of the division of the cerebral cortex into three main territories, of which we consider the cortex intermedius structurally and genetically an area of transition between the cortex completus and the cortex incompletus.

The lateral intermediate subregion, *etl*, separating the central entorhinal subregions from the isocortex throughout almost its entire extension, is similar in the early stages to the subregion *etp* (rarefaction of the *m* layer). In later stages a wedge-shaped darkening of the *m* layer in the direction of the isocortex (fig. 3, *etl*) is characteristic of the greater middle part of subregion *etl*. This wedgelike shape is clearly seen in the adult brain also, though not so strongly pronounced. As regards other features of the subregion *etl*, it should be noted that layer *ext* possesses here no papillary structure and the cortical plate fails to show a true stratum dissecans, differing in this respect from adjacent entorhinal formations, and that, on the other hand, it presents (in contrast to the isocortex) discontinuity in structure of layer *ext* and absence of layer IV.

On the whole, Ammon's plate within the entorhinal region is separated from the isocortical plate as distinctly as it is within the presubiculum region. This separation is effected by the presence of stratum *Diss*² (formations *epr*¹ and *epr*², fig. 3) or by the presence of stratum interlaminare (formation *ea* β , fig. 3). Superlamination is particularly clear here, as represented by *limes duplex*, e. g., by free termination of Ammon's plate, which disappears in the subjacent white matter at the border of the entorhinal region (fig. 3, *ea* β —*etl*). It is true that *limes duplex* becomes effaced in the late stages, as a result of continuous migration of neuroblasts into the isocortex, where they subsequently form its extreme layer, merging with the internal layer of the entorhinal cortex. Thus, the extreme internal layer of the isocortex seems to correspond here to Ammon's plate—essentially layer VI of the isocortex, the fifth one corresponding in part to stratum *Diss*² (V b) and in part to stratum interlaminare (V a). It must, however, be emphasized that this conformity arises only secondarily at a comparatively late stage of ontogenesis.

The perisemicortical zone (insular intermediate region) is in some respects similar to the periarchicortical one: that is, it also consists of a number of formations (*ii*, *ia*, *il*, *ii*², *ii*¹, *ii*⁰) which effect a successive, though interrupted, transition (these formations are sharply separated from each other) from the cortex incompletus (here semicortex) to the cortex completus. The formation *ii*, which is the one nearest the isocortex, is characterized in early stages by a wedge-shaped widening of the cortical plate in the direction of the isocortex, while the formation *ii*⁰, which is the one nearest the semicortical zone, presents strong rarefaction of the cortical plate (fig. 6). In the adult the formation *ii*⁰ is far from being so rarefied, but it is still well differentiated from surrounding formations by its looseness and extreme effacement of stratification.

Other, and quite essential, features are also concerned in the similarity between the insular intermediate layer and the entorhinal region, a similarity which is in full conformity with our concept of unification of the perisemicortical and the periarchicortical zone as the cortex intermedius and with our subdivision of the entire cerebral cortex into three, and not into the traditional two, main territories. A wedge-shaped transition of the isocortex into intermediate formations (figs. 3 and 5, *etl* and *ii*) occurs in both cases. The structure of the stratum interlaminare, so typical of entorhinal formations, is quite similar to the structure of the intermediate layer (V a of some authors) of the insular formations *ii*², *il* and, in part, *ii*. Finally, the typical splitting of the cortical plate in the entorhinal region, revealing its transitional character, may, with full justification, be compared to the presence of the claustrum in the insular region.

As a matter of fact, our ontogenetic investigations have disclosed that the claustrum cannot be considered either as a derivative of the cortical plate, as some believe, or as a formation genetically similar to the striatum or to the nucleus amygdalae, as others hold; it is to be regarded, rather, only as an intermediate formation. Whereas the striatum and the amygdalar region are immediately connected with the matrix, and the cortical plate presents in the region of the isocortex and archicortex an accumulation of neuroblasts on the surface of the end brain, separated from periventricular cell masses, the claustrum is separated from the matrix and, at the same time, represents the result of an accumulation of neuroblasts, the chief mass of which failed to reach the cortical plate in the process of their migration and were arrested a certain distance between the cortical plate and the striatum. In the early stages the claustrum is actually involved in a dense, diffuse accumulation of neuroblasts (zone *R* according to our terminology; fig. 5), which is continuous with the cortical plate. However, there is

no reason to regard zone *R* (continuing into the nucleus amygdalae immediately!) as the internal layer of the cortical plate, because this zone, like the intermediate layer (*z*) in the isocortical region, represents only

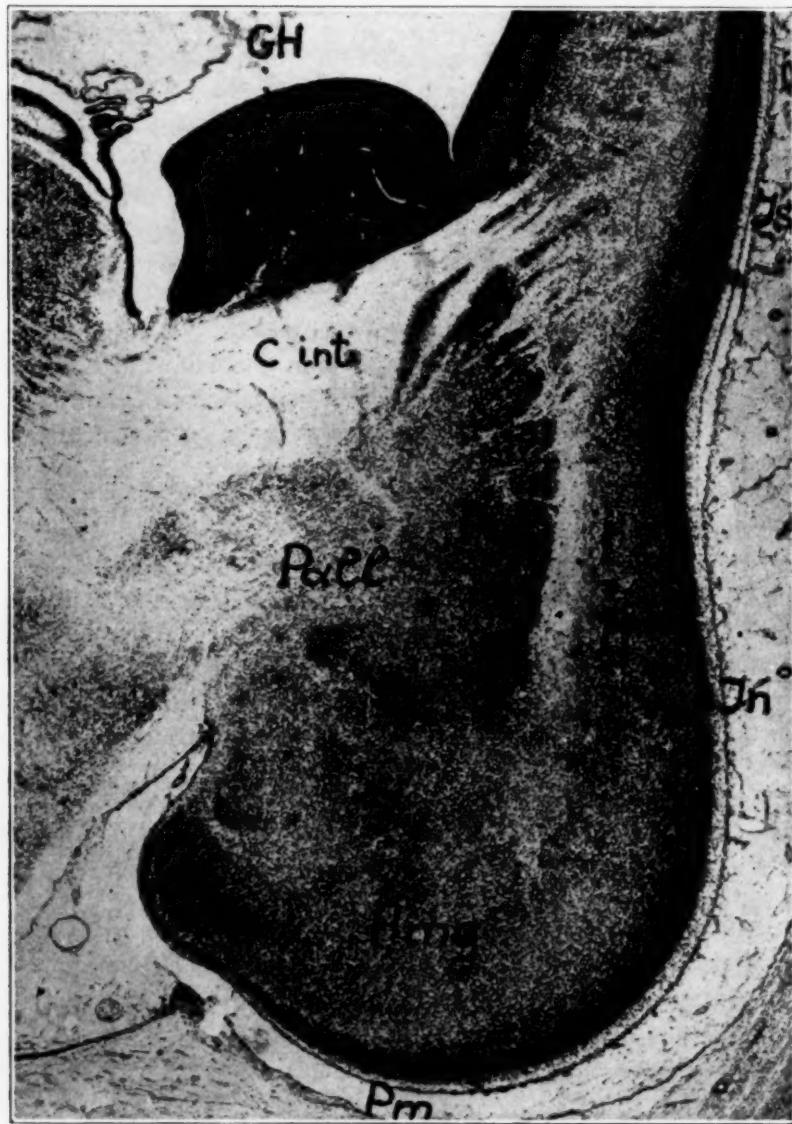


Fig. 5.—Stage, 55 mm. *Amg* indicates nucleus amygdalae; *C int*, internal capsule; *Gh*, Hügel's ganglion; *In*, insular region; *Is*, isocortex; *Pall*, pallidum; *Pm*, periamyg达尔 region; *Put*, putamen; *R*, zona *R*, including claustrum and continuing into nucleus amygdalae.

a zone of migration of neuroblasts, and by no means a zone of their stabilization, as is to be expected of a true cortical plate.

Correlations in the region of the allocortical zones *sensu strictiori* are considerably simpler than those in the region of the cortex intermedius.

The archicortical zone is already differentiated in an early stage into the subiculum (*Sub*), the cornu ammonis (*CA*) and the fascia dentata (*FD*), while the cornu ammonis is divided into sectors h^1 to h^5 ; all these formations (except the fascia dentata [*FD*]) continue, showing structural modifications, over the corpus callosum (*tenia tecta*). The subdivision into distinct formations is effaced orally, in the supracallosal and subgenual portions. The same correlations are also seen in the adult brain. This stability of differentiation into separate formations, together with the stability of general structural features, is characteristic of the



Fig. 6.—Stage, 130 mm. *Cl*, claustrum; *D*², regio diagonalis; *ii°* and *ii*, perisemicortical formations; *Pp*¹ + *Pp*², regio prepiriformis; *T*¹ and *T*², tuberculum olfactorium.

archicortex, in contrast to the cortex intermedius and, particularly, with the entorhinal region.

The semicortical regions—the tuberculum olfactorium (fig. 6, *T*) and the regio diagonalis—are characterized by still greater stability and in all the stages reveal differentiation into typical formations, *T*¹ and *T*², *D*¹ and *D*² (fig. 6).

The changes in the periamygdalar region are more considerable. In early stages it consists of four formations, elongated orocaudally and parallel to each other: *Pe*, *Pml*², *Pml*¹ and *Pmm*, which show transitions into the prepiriform region through intermediate formations *Ppl*²,

*Ppl*¹ and *Ppm*. The same subdivision is maintained at later stages in the caudal part, while in the oral part *Pml*² and *Pml*¹ no longer exhibit differentiation and show transition into a common formation *Pml*³, the last passing into a common intermediate formation, *Ppl*, which no longer shows subdivision into *Ppl*¹ and *Ppl*², as it does in early stages.

The problem of development of the periamyg达尔 cortex is closely connected with the problem of the genesis and nature of the nucleus amygdalae.

According to our investigations, the amygdalar complex is not to be considered as a modified and thickened part of the temporal cortex which has separated from the latter and embedded itself in the depth of the subcortex, but it is also inadmissible to contrast it with the periamyg达尔 formations. The entire process of development obviously shows that the periamyg达尔 cortex belongs to the cortex semiseparator in our sense, e. g., to the zone where the cortical plate shows incomplete separation from the periventricular cell masses—in our particular case, from the nuclei of the amygdala, which fully belong to these masses (fig. 5).

The prepiriform region presents similarity to the insular region in that here, also, the cortical plate is situated over the claustrum (fig. 6, *Pp*) ; however, correlations show here much more stability in the process of evolution than in the insular region, and its structure presents essential differences both with respect to the marginal layer and to the cortical plate. Beginning from 130 mm. (or somewhat earlier) and covering the whole process of further development, this region shows subdivision into four formations: *Pp*¹, characterized by a compact, narrow and tortuous cortical plate; *Pp*², which occupies the gyrus olfactorius lateralis and is characterized by a very wide layer I and a rarefied cortical plate, and *Pp*^{2a} and *Pp*^{2b}, presenting a transition from the chief formation, *Pp*², to the chief formation, *Pp*¹. A similar subdivision is seen in the prepiriform region of the adult brain also.

Important is the problem of conformity of the development of the allocortical and periallocortical formations, or the cortex incompletus and the cortex intermedius, respectively, with the fundamental biogenetic law. The process of development of the semicortical zone is in full accordance with this law. This region, which is phylogenetically the oldest (paleocortex) and closest to the oldest type of end brain structure (presence of periventricular cellular masses alone), is, at the same time, the first to develop in the process of ontogenesis. Correlations in the archicortical zone are much more complex. Unexpectedly, the cortical plate is here differentiated not earlier, but later, than in the decidedly phylogenetically younger isocortical plate (neocortex). However, the development of the archicortical or Ammon's zone is completed earlier than that of the isocortex, which means that on the whole its development presents a considerably shorter course than that of the isocortex.

The differentiation of cellular elements generally starts in the cortex incompletus and the cortex intermedium earlier than in the cortex completus, though this varies in different regions. Here, also, as in the isocortex, the initial rate of evolution by no means always conforms with the definitive size of the corresponding cells.³ Ammon's zone is of particular interest in this respect. Here, the cells in formation h^2 begin to increase in size much earlier than the cells in formation h^4 and h^5 , although the cells in formation h^4 and h^5 are in the adult but slightly smaller than those in formation h^2 .

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PHYSIOLOGY AND THERAPY OF CONVULSIVE DISORDERS

I. Effect of Anticonvulsant Drugs on Electroshock Seizures in Man

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THE EFFECTS of drugs on various properties of electroshock seizures in experimental animals have been described in previous communications from this laboratory.¹ Many anticonvulsant drugs in nontoxic doses have been found to modify the seizure pattern, usually by shortening or abolishing the tonic phase. A simple and quantitative method of assay of anticonvulsant drugs has been developed on the basis of this selective action.¹¹ Of the more widely used antiepileptic agents, diphenylhydantoin, phenobarbital and "tridione" (trimethadione) rank

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as named in decreasing order of effectiveness when examined by this method.

It would seem important to determine whether the pattern of electroshock seizures in man can be modified by anticonvulsant drugs in doses known to be clinically effective in epilepsy. Such information might help to elucidate the mechanism of action of drugs in control of convulsive disorders. The common use of electroshock seizure therapy of certain psychiatric disorders provides an opportunity for such observations on nonepileptic subjects. Although a number of investigators have studied the ability of barbiturates, diphenylhydantoin and other agents to raise the electroshock seizure threshold in man,² only desultory attention has been paid to the modification of the seizure pattern by these drugs. It has been observed^{2b} and confirmed^{2d} that patients given premedication with diphenylhydantoin have a greater than normal incidence of atypical seizures. A brief comment on the ability of diphenylhydantoin to shorten the tonic phase in man^{2b} antedates similar observations on animals.³

The present communication is concerned chiefly with the relative ability of some commonly used anticonvulsant drugs to alter the seizure pattern in patients receiving electroshock therapy. The work was undertaken in order to extend our investigations from animals to man and to examine the possibility of developing a simple method of assay of the action of anticonvulsant drugs in man.

MATERIALS AND METHODS

The Offner and Rahm 60 cycle, alternating current instruments were used for electroshock therapy. The strength of the stimulating current ranged from 500 to 750 milliamperes and the duration of the stimulus from 0.2 to 0.4 second. The various components and the total duration of each seizure were timed to the nearest second. Control

2. (a) Challiol, V.: L'azione del luminal nella crisi convulsiva da elettroshock, *Riv. sper. di freniat.* **64**:635, 1940. (b) Hemphill, R. E., and Walter, W. G.: Epanutin and Electric Convulsion Therapy, *Lancet* **1**:446-448, 1941. (c) Kalinowsky, L. B., and Hoch, P. H.: Shock Treatments and Other Somatic Procedures in Psychiatry, New York, Grune & Stratton, Inc., 1946. (d) Kalinowsky, L. B., and Kennedy, F.: Observations in Electric Shock Therapy Applied to Problems of Epilepsy, *J. Nerv. & Ment. Dis.* **98**:56-67, 1943. (e) Rubinstein, H. S.: The Use of Pentothal Sodium as a Psychomotor Depressant in Electro-Shock Therapy, *Dis. Nerv. System* **6**:242-244, 1945.

3. Delay, J., and Soulairac, A.: Action comparée des barbituriques, des hydantoines, et des bromures sur l'épilepsie électrique du rat, *Compt. rend. Soc. de biol.* **138**:60-61, 1944. Goodman, Swinyard and Toman.^{1a} Goodman and Toman.^{1d} Toman, Swinyard and Goodman.^{1j}

observations were made on 22 male and 14 female adult psychiatric patients. Of these, 15 men and 7 women were chosen for a study of the effects of drugs on the seizure pattern. The following agents and dosage schedules were used:

1. Diphenylhydantoin sodium ("dilantin sodium") : 0.4 to 0.8 Gm. daily for four days.
2. Phenobarbital: 0.3 to 0.4 Gm. daily for one to three days.
3. "Tridione"⁴ (trimethadione; 3, 5, 5-trimethyloxazolidine-2, 4-dione) : 2.4 to 3.6 Gm. daily for two to three days.
4. Sodium bromide: 6.0 to 9.0 Gm. daily for one week. The serum bromide level was determined just prior to the electroshock test.
5. "Mebaral" (*N*-methyl, 5-ethyl, 5-phenyl barbituric acid) : 0.8 to 1.2 Gm. daily for three days.
6. "Mesantoin"⁵ (*N*-methyl, 5-phenyl, 5-ethyl hydantoin) : 0.4 to 0.6 Gm. daily for four days.

It was intended that the lower dose of each drug should fall within the customary range for antiepileptic medication and that the higher dose should exceed this range.

RESULTS

Control Seizures.—A total of 67 electroshock seizures were observed in 36 patients without prior administration of drugs. The initial control seizures elicited in these patients are presented graphically in figure 1, in which the results are arranged in order of decreasing duration of the tonic phase. The total duration of the seizure is calculated from the time of onset of the tonic phase because of the great variation in the latent period⁶ (mean, five seconds; range, one to thirty seconds). Calculated in this way, the total duration of the seizure is the most constant property of electroshock convulsion in man (mean, 36 seconds; range, 27 to 43 seconds; standard deviation, 4 seconds); it does not appear to be related either to the latent period or to the duration of the tonic phase. The duration of the tonic phase was more variable

4. "Tridione" was supplied by Dr. R. K. Richards, of the Abbott Laboratories, North Chicago, Ill.

5. "Mesantoin" was supplied by Mr. S. M. Fossel, Sandoz Chemical Works, Inc., New York.

6. In animal experiments, the duration of the latent period is inversely related to the excess of current above threshold and approaches a limiting value of two seconds.¹³ Long latent periods in electroshock seizures in man probably indicate that the current did not greatly exceed threshold.^{2c} In the present series of patients, it was not found feasible to use intensities of current as far above threshold as those employed to insure maximal seizures in animals.¹³

(mean, 13 seconds; range, 4 to 24 seconds; standard deviation, 4 seconds). Although an extensor component of the tonic phase comparable to that seen in experimental animals¹³ was demonstrable in most patients, the sequence of postural changes within the tonic phase was rather variable, even in the same patient during consecutive trials. Therefore no attempt has been made to subdivide the tonic phase in this report. No significant sex difference was observed in the pattern or duration of seizures.

In figure 2 are shown two consecutive control seizures in each of 11 patients. The threshold for tonic-clonic seizures was definitely increased in only 2 patients on second trial. The pattern and duration

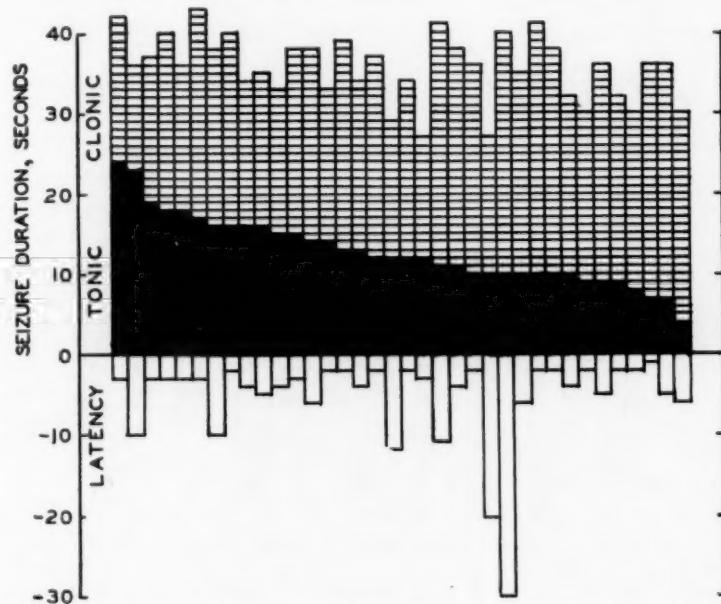


Fig. 1.—Pattern and duration of initial control electroshock seizures in 36 patients, arranged from left to right in order of decreasing duration of the tonic phase. In this figure, and in the accompanying figures, the duration of seizures was calculated from the onset of the tonic phase, which is shown in solid black. The clonic phase is represented by cross hatching. The latent period is timed from administration of the stimulus to onset of the tonic phase and is shown by open rectangles below the base line. The electroshock current ranged from 500 to 700 milliamperes, and the duration of stimulation, from 0.2 to 0.4 sec.

of seizures in these and in subsequent control trials provided a basis of reference for the effects of drugs.

In classifying electroshock seizure patterns in man, the following difficulty in interpretation was frequently encountered. After receiving a shock which fails to produce a tonic-clonic seizure, the patient often exhibits apnea, signs of confusion and automatism for a minute or

longer. Such activity resembles a psychomotor seizure or ictal automatism,⁷ but has been given various names, such as "petit mal" or "subconvulsive response."^{2c} That this phenomenon is indeed a seizure is attested by the following observations: 1. If a second shock of the same intensity and duration of current as the original is given within about fifteen seconds of the "missed shock," a major tonic-clonic seizure usually develops. We have found in experimental animals that true summation of inadequate stimuli can occur only with stimulus intervals of two seconds or less; however, if the first shock produces only electroencephalographic evidence of seizure activity, a second shock of the same intensity given at any time during such activity can then cause the appearance of an overt "clinical" seizure.⁸ 2. Even without a second shock the patient may ultimately exhibit

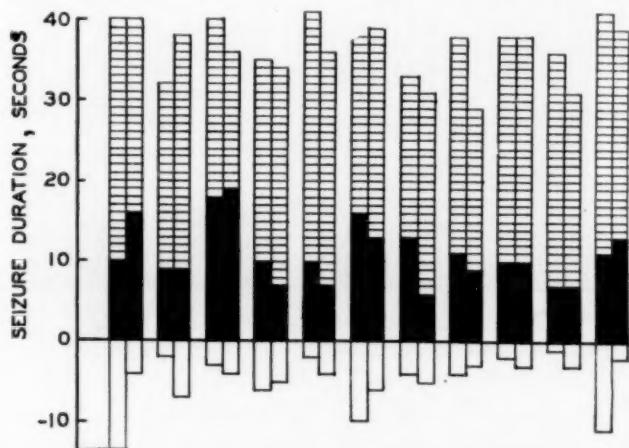


Fig. 2.—Variability of control electroshock seizures elicited in 11 patients. Each pair of columns represents the pattern and duration of seizures occurring during two consecutive treatments, given two days apart. This graph is to be compared with subsequent figures showing effects of drugs.

a major seizure. Latent periods as long as ninety seconds have been observed; other instances of long delay are seen in figure 1. 3. If the second shock is withheld for several minutes after a "petit mal" seizure, the duration and intensity of current must often be considerably increased in order to produce a tonic-clonic seizure. In accordance with our observations on animals, this may indicate postseizure refractoriness following a "subclinical" seizure discharge in the electroencephalogram. Such a subclinical electroencephalographic discharge in

7. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941.

8. Toman, J. E. P.; Swinyard, E. A., and Merkin, M.: Unpublished data.

animals resembles the pattern of spontaneous human psychomotor seizures but is quite unlike a petit mal record.

Because of these considerations, we have preferred to classify any electroshock response consisting of apnea, confusion and automatism as a psychomotor seizure.

Modification of Seizures by Drugs.—For convenience in analyzing the action of a drug, only three types of seizures were considered: (a) psychomotor seizures (as previously described); (b) clonic seizures (with no initial tonic phase), which were never observed in patients not receiving medication; (c) tonic-clonic seizures (typical electroshock convulsions with an initial tonic phase), which could always be elicited

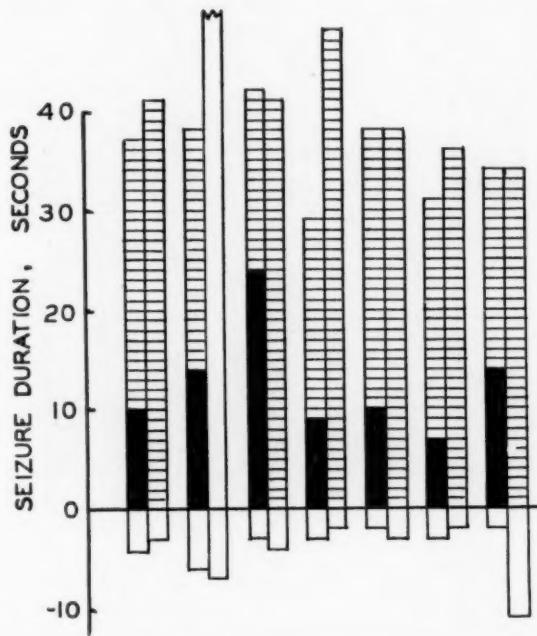


Fig. 3.—Effects of diphenylhydantoin on the pattern and duration of electroshock seizures in 7 patients. The first column in each pair represents the control seizure; the second, the seizure after a course of diphenylhydantoin medication. Observe that the tonic phase is abolished in all cases. The open column in the second pair from the left denotes a psychomotor seizure of long duration. The first 3 patients (starting at the left of the figure) received 0.4 Gm. of diphenylhydantoin sodium daily for four days; the next 3 patients, 0.6 Gm. daily, and the remaining patient, 0.8 Gm. daily.

in patients without medication within the range of intensity of the current of the electroshock apparatus.

No attempt was made to measure the threshold for minimal (psychomotor) seizures. Rather, the ability of each drug to prevent the appearance of typical tonic-clonic seizures was taken as the criterion of anticonvulsant action.

Diphenylhydantoin: Of 7 patients receiving diphenylhydantoin and retested with the control electroshock current and duration, the seizures were clonic throughout in 3 and psychomotor in 4. When the electroshock current and duration were increased with the latter 4 patients, clonic convulsions occurred in 3. The fourth patient again exhibited only a psychomotor seizure, but a facial clonic component was present. Figure 3 illustrates these results. Diphenylhydantoin consistently abolished the tonic phase of the convulsions. In the doses employed the drug caused no toxic effects.

Phenobarbital: Figure 4 illustrates the results obtained with 7 patients receiving phenobarbital. Two patients receiving the higher

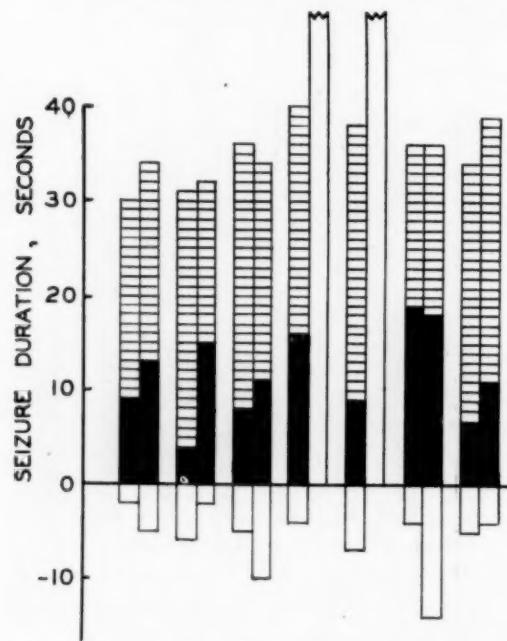


Fig. 4.—Effects of phenobarbital on the pattern and duration of electroshock seizures in 7 patients. The first column in each pair represents the control seizure; the second, the seizure after a course of phenobarbital medication. The first 3 patients (starting at the left of the figure) received 0.3 Gm. of phenobarbital for one day; the remaining 4 patients, 0.4 Gm. daily for three days.

dose reported that the drug caused vertigo and sedation, and in these 2 subjects only psychomotor seizures of long duration were elicited despite an increase in stimulating current. The remaining 5 patients did not show any toxic or depressant effect of phenobarbital. Tonic-clonic seizures were obtained in 2 of these 5 patients only after the stimulating current was increased. In the remaining 3 patients, such seizures were obtained with the intensity of current and duration of

stimulus used in the control seizure. The results indicate that after nontoxic doses of phenobarbital a tonic-clonic seizure may still be elicited, although an increase in the electroshock current or duration may be required.

"Tridione" (Trimethadione): Figure 5 illustrates the results obtained with 8 patients receiving trimethadione. None complained of toxic effects from the doses employed. The drug did not increase the threshold for tonic-clonic seizures.

Sodium Bromide: The results of administration of sodium bromide for 9 patients are given in figure 6. The serum bromide levels at the

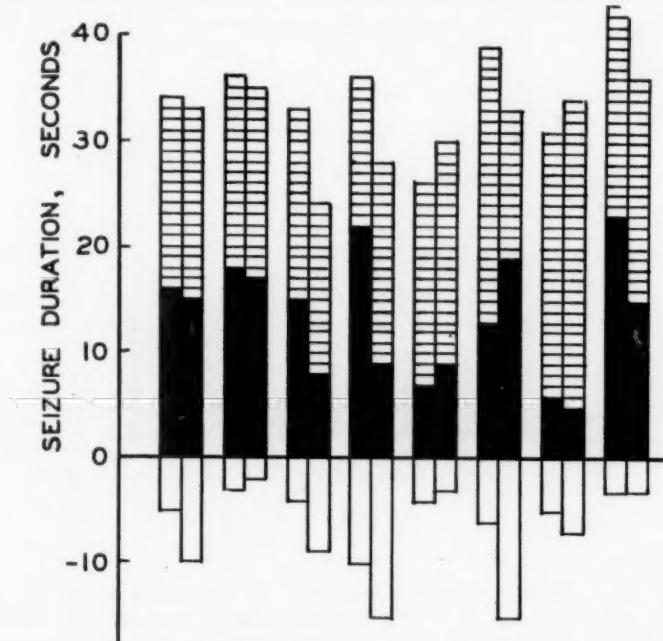


Fig. 5.—Effect of "tridione" (trimethadione) on the pattern and duration of electroshock seizures in 8 patients. The first column in each pair represents the control seizure; the second, the seizure after a course of trimethadione medication. The first 4 patients (starting at the left of the figure) received 2.4 Gm. of trimethadione daily for two days; the next patient, 3.6 Gm. daily for two days, and the last 3, 3.6 Gm. daily for three days.

time of the electroshock observations ranged from 135 to 235 mg. per hundred cubic centimeter (13 to 23 milliequivalents per liter of bromide). Nausea and an acneform rash were observed in 1 patient and sedation in 3 others. These signs bore no definite relation to the serum bromide level. The threshold for tonic-clonic seizures was definitely increased in 3 of the patients with toxic symptoms and in 1 other. In 2 of these patients the tonic-clonic seizures could be obtained with the maximum

intensity of current and duration of shock available, but the tonic phase was shortened by more than 50 per cent as compared with previous controls. In a third patient only a psychomotor seizure was obtained, and in a fourth the severest convulsion elicited was purely clonic throughout.

"Mebaral" (*N*-methyl, 5-ethyl, 5-phenyl barbituric acid): The results of medication with "mebaral" are illustrated in figure 7. In 6 patients receiving the lower dose of "mebaral" (0.8 Gm. daily for three days) there was no evidence of modification of the seizure pattern or of elevation in threshold for tonic-clonic seizures. No toxic signs were observed. In 3 other patients receiving 1.2 Gm. of "mebaral" daily

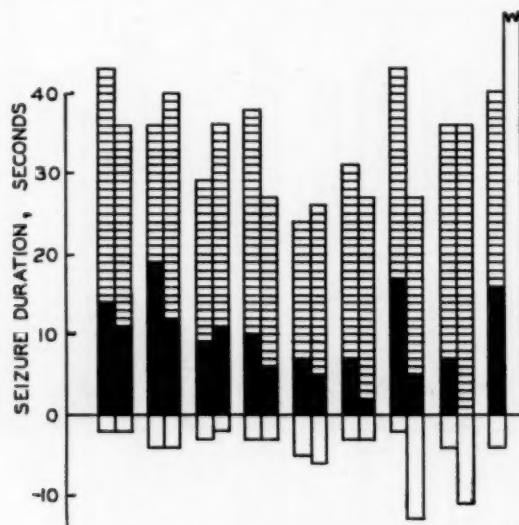


Fig. 6.—Effect of sodium bromide on the pattern and duration of seizures in 9 patients. The serum bromide levels for these patients ranged from 135 to 235 mg. per hundred cubic centimeters (13 to 23 milliequivalents per liter of bromide). The values for individual patients (left to right) were 235, 208, 172, 135, 170, 160, 200, 197 and 164 mg. per hundred cubic centimeters.

for three days there was definite sedation. Only psychomotor seizures could be obtained in 2 of these 3 patients.

"Mesantoin" (*N*-methyl, 5-phenyl, 5-ethyl hydantoin): Of the 4 patients receiving 0.4 Gm. of "mesantoin" daily for four days, 1 complained of vertigo and was found to have a slight elevation in temperature. Several weeks later this patient was placed under treatment with the higher dose of "mesantoin," without untoward effects. None of the 4 patients showed alteration in type of seizures or elevation in threshold for tonic-clonic seizures. Seven patients received 0.6 Gm. of "mesantoin" daily for four days, with no signs of toxicity. The threshold for

tonic-clonic seizures was definitely increased in 5 of the patients. Four of these sustained only psychomotor seizures. In the fifth only a purely clonic seizure could be obtained.

COMMENT

The most consistent finding in the present investigation was the ability of diphenylhydantoin to abolish the tonic phase of electroshock seizures in man. Purely clonic convulsions were never observed in control patients but were typically present in patients receiving diphenylhydantoin in doses within the therapeutic range for epilepsy. One might ask whether the same action by which this drug modifies the electroshock pattern in normal man can account for the prevention of spont-

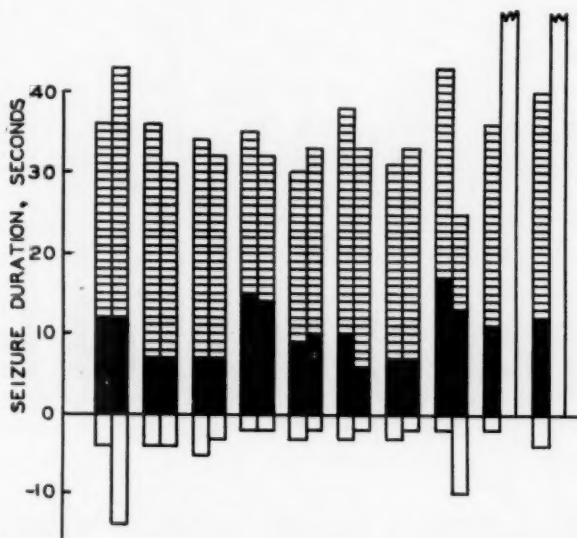


Fig. 7.—Effect of "mebaral" (*N*-methyl, 5-phenyl, 5-ethyl barbituric acid) on the pattern and duration of electroshock seizures in 10 patients. The first 7 patients (at the left of the figure) received 0.8 Gm., and the remaining 3 patients 1.2 Gm., of "mebaral" daily for three days.

taneous seizures in epileptic patients. The therapeutic mechanism would appear to be something other than an increase in seizure threshold. Previous experimental observations in animals have demonstrated the inability of diphenylhydantoin to raise the normal threshold to electroshock seizure.⁹ This does not exclude the possibility that diphenylhydantoin may act clinically by elevating abnormally lowered thresholds toward normal levels. Such an effect has been demonstrated experi-

9. Goodman, Swinyard and Toman.^{1a-c} Goodman, Toman and Swinyard.^{1e} Swinyard and Goodman.^{1f} Toman, Swinyard and Goodman.^{1j}

mentally in rats whose threshold for electroshock seizures was decreased by depletion of extracellular electrolyte.¹⁰ However, diphenylhydantoin is less effective in this respect than other anticonvulsants, including phenobarbital and trimethadione.

Another possible mechanism deserves mention. We have previously pointed out that electroencephalographic records of seizures in animals are considerably modified by diphenylhydantoin. In particular, the frequency of spike discharges characteristic of maximal seizures is much reduced.¹¹ "Spike" activity is commonly observed as a focal disturbance in the interseizure electroencephalographic records of patients with a history of convulsions. It is conceivable that diphenyl-

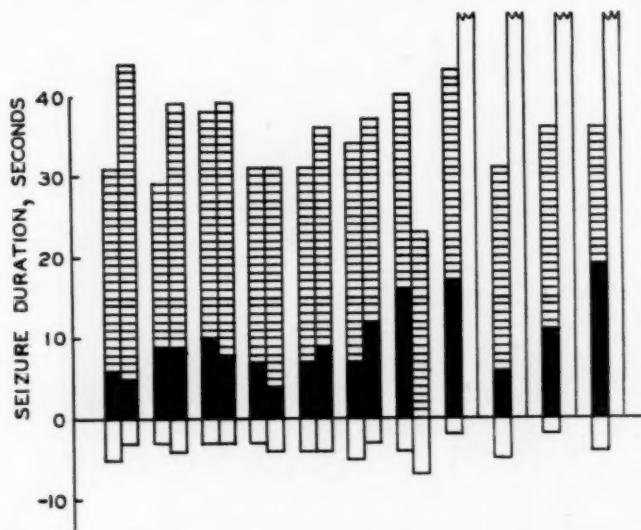


Fig. 8.—Effect of "mesantoin" (*N*-methyl, 5-phenyl, 5-ethyl hydantoin) on the pattern and duration of electroshock seizures in 11 patients. The first 3 patients (starting at the left of the figure) received 0.4 Gm. of "mesantoin" daily for four days; the remaining 8 patients, 0.6 Gm. daily for four days.

hydantoin may act by preventing these isolated "spike" discharges from attaining high frequency and spreading to normal cerebral tissue.

No systematic study of the effect of drugs on the threshold for minimal psychomotor seizures in human subjects was attempted in this investigation. Such a study entails the use of intensities of current which fail to evoke convulsions. The psychic trauma of subconvulsive stimulation is usually believed to detract from the salutary effects of electroshock therapy. Although some anticonvulsant drugs, including trimethadione and phenobarbital, have been shown to produce

10. Swinyard, Toman and Goodman.^{12, 13}

a moderate increase in threshold for electroshock convulsions in experimental animals, diphenylhydantoin fails to do so. On the basis of observations on animals, we have previously suggested that the clinical value of an anticonvulsant drug need not be correlated with ability to increase the normal threshold for electroshock seizures.¹¹

The doses of drugs used in this investigation were within or above the usual range for the therapy of clinical seizures. Inasmuch as adequate doses of trimethadione failed to alter the pattern or the threshold of seizures, it can only be concluded that the specificity of action of this drug on petit mal is dependent on some property other than those investigated. Among the other properties of trimethadione which have been investigated in animals, the preeminent one is its ability to protect against drug-induced seizures and slow wave electroencephalographic dysrhythmias. The relation between these actions of trimethadione and its specificity of action in petit mal has been discussed in full elsewhere.¹²

The limited data in this series do not permit an accurate comparison of anticonvulsant potency. With more patients and a wider range of medication, it would be possible to determine the dosage level (T) producing toxic signs in 50 per cent of patients, and the dose (P) preventing the appearance of a tonic phase in 50 per cent of patients. A protective index (T/P) could then be calculated, as in previous observations on animals.¹³ The present data suggest that the index for diphenylhydantoin would be considerably greater than 1.0 and that "mesantoin" would also rank high. Phenobarbital, sodium bromide and "mebaral" would probably rank together, with an index close to unity. The results with trimethadione are inconclusive, since neither toxic nor effective levels were reached, although the doses employed were more than adequate for the control of clinical petit mal.

In conclusion, the present data seem sufficiently encouraging to justify the use of human subjects for a quantitative comparison of the action of anticonvulsant drugs.

SUMMARY

Data are presented on the ability of anticonvulsant agents to prevent tonic-clonic seizures in nonepileptic patients undergoing electroshock therapy.

Diphenylhydantoin in nontoxic doses consistently abolishes the tonic phase of electroshock seizures. "Mesantoin" (*N*-methyl, 5-phenyl, 5-ethyl hydantoin) also ranks high in ability to modify the pattern of

11. Goodman, Swinyard and Toman.^{1b} Goodman, Toman and Swinyard.^{1e} Swinyard and Goodman.^{1f} Swinyard, Toman and Goodman.^{1h} Toman, Swinyard and Goodman.^{1j}

convulsions. Phenobarbital, sodium bromide and "mebaral" (*N*-methyl, 5-phenyl, 5-ethyl barbituric acid) are effective, but only in doses which occasionally produce undesirable side effects. "Tridione" (trimethadione) is ineffective in modifying the electroshock seizure pattern when given in doses more than adequate to control clinical petit mal epilepsy.

It is suggested that the modification of the electroshock seizure pattern in man offers a convenient method for the evaluation of potentially useful anticonvulsant drugs.

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INFLUENCE OF ANXIETY ON ATTENTION, LEARNING, RETENTION AND THINKING

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IN THE investigation of the influence of emotions on psychologic functions by one of us (O. D.), it became apparent that the technical characteristics of many of the tests used more or less commonly by psychiatrists were not known. Consequently, a preliminary study was made to determine the reliability and other characteristics of several of these tests. These results are reported in the first part of this paper, whereas in the second part the results of the influence of anxiety on some of the tests are given. In the third part, the application of these results to the customary psychiatric examination is reviewed.

TECHNICAL CHARACTERISTICS OF SOME CLINICALLY USED TESTS

In order to be able to investigate the psychopathologic influences of anxiety on intellectual functions, tests were chosen for the study of attention, learning, retention, memory and thinking. Tests were selected which have been used in psychopathologic research work and in clinical psychiatry. Test scores were obtained in some cases from normal women college students and in some cases from psychiatric patients of the type on whom it was desired to use the tests later for further research.

Attention.—Although the concept of attention is greatly disputed in present day psychology, attention and its disorders have maintained an important place in psychopathology and clinical psychiatry. In our investigations, we were forced to consider the Wundtian distinction between active and passive attention because of the claim of leading psychopathologists that various mental disorders affect these two types of attention independently.¹ These authors distinguish between an

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Miss D. Kearton, Miss M. Jackson and Miss M. Guy assisted in collecting part of the data on this experiment.

1. Bleuler, E.: *Lehrbuch der Psychiatrie*, ed. 7, Berlin, Julius Springer, 1943.

"active" type of attention, in which the person directs his attention to the object, and a "passive" type, in which he receives stimuli without specifically intending to do so.

The tests selected for study were those published by Franz² for determining the fluctuations of attention with simple and complex stimuli and the digit repetition test.

1. Fluctuations of Attention with Simple Stimuli (Franz,² page 78): Two tests were selected in which "a series of numerals or letters is read to the patient in a monotone at the rate of one each half second and the subject is instructed to tap or make some other movement whenever a definite letter or digit is read." This test was given to 48 college students and proved to be too easy and to have too little reliability to be of further usefulness. It was therefore discarded.

2. Digit Span: The oral digit repetition test has long had a place in modern tests of intelligence, and ability at this simple task is known to vary with intelligence. However, when scored in a different way, it may be taken also as a measure of attention if it is assumed that faulty attention causes failures which occur before the point at which the subject has reached the absolute limit in length of series of digits which he can repeat. Thus, anxiety might conceivably affect the results of the test in either or both of two ways: It might increase the number of failures before the maximum limit was reached (attention) and/or it might decrease the actual maximum limit (intellectual ability).

3. Fluctuations of Attention with Complex Stimuli (Franz,² page 79): Under this heading, Franz presented a test in which "the experimenter reads a story to the subject who is instructed to react [by tapping or by repeating the word] whenever he hears a certain word [barn]." The story was divided into 44 logical units, and the subject was asked to repeat as much of the story as he could immediately after the reading and without prior warning. It was felt that the amount retained might be used as a measure of passive attention, while the tapping fixed active attention. This test was given to 47 students. The corrected odd-even reliability coefficient for the number of units retained was 0.89. The "Barn Story," with the units indicated, follows:

1	2	3
When a boy,/ at every possible opportunity/ I went to the <i>barn</i> / in which		
4	5	
there were not only various implements/ used about the farm/ but a variety of		
6	7	8
old tools/ and machinery/ which had been stored there/ for many years./ The		
10	11	12
<i>barn</i> was high/ and had three stories/ which originally were used for many pur-		

2. Franz, S. I.: *Handbook of Mental Examination Methods*, ed. 2, New York, The Macmillan Company, 1919.

poses./ It had been built fifty years/ before I was born./ The old inhabitants
said/ that when it was built/ the *barn* was the best known/ in the country/ and,
although other *barns*/ of greater size/ and of more ornate appearance/ had been
erected/ in more recent years,/ they still continued to talk of it/ as one of the
most wonderful buildings/ in existence./ The building had been used/ for other
purposes/ than that of a *barn*./ It contained/ a wonderful collection/ of tools/
of all kinds/ and several neat workshops/ that were well stocked/ with woods/
of all kinds./ Adjoining it was a *barnyard*/ laid out at a later date/ but with
small houses/ for the chickens/ and ducks/ which were miniatures/ of the large
barn building./

Learning and Retention.—Learning and retention were studied by means of two stylus mazes. Each maze consisted of a single correct path, with five blind alleys. Maze 1 had 24 turns; maze 2 had 29. The subjects were trained to the criterion of three successive errorless trials, or for a period of seventy-five minutes if they had not reached the criterion by that time. They were retrained twenty-four hours later on the same maze to the same criterion. Errors were scored in the usual manner, and the corrected odd-even reliability coefficient for error scores for maze 1, in both the original and the relearning test, was 0.86; and for maze 2 they were 0.90 and 0.94.

In order to determine whether the two mazes were of equal difficulty, and whether if the experience of learning one maze would carry over for as long as six weeks in such a way as to facilitate the learning of the second maze, maze 2 was given to 30 psychoneurotic and depressed patients six weeks after maze 1 had been learned successfully, while to another group of 30 psychoneurotic and depressed patients maze 2 was given first, followed six weeks later by maze 1. It was found that the two mazes are of practically equal difficulty and that there was no appreciable carry-over of maze learning ability from one test to the other, as measured by errors, number of trials or speed.

Immediate Memory.—The fixation of new impressions was first determined by using two brief paragraphs from the Thorndike-McCall Reading Scale (stories of Dick and of Nell). Both stories were far too easy and had too few units. The odd-even reliability coefficients were not greater than their probable errors. This test was therefore abandoned.

The "Cowboy Story," which is used in psychiatric examination (from the original 1916 Stanford-Binet scale), gave better results. The story

was divided into 27 logical units. This test was given to 31 patients. The corrected odd-even reliability coefficient for the number of units retained was 0.94. The "Cowboy Story" can be used as a reliable means of discriminating between patients on the basis of immediate memory. The story, with the units used, follows.

1 2 3 4 5
 A cowboy/ from Arizona/ went to San Francisco/ with his dog,/ which he
 6 7 8 9
 left/ at a friend's/ while he purchased/ a new suit of clothes./ Dressed finely,/ he
 10 11 12 13 14
 went back/ to the dog,/ whistled to him,/ called him by name/ and patted him./
 , 15 16 17
 But the dog would have nothing to do with him,/ in his new hat/ and coat,/ but
 18 19 20 21
 gave a mournful/ howl./ Coaxing was of no effect/; so the cowboy went away/
 22 23 24 25
 and donned his old garments,/ whereon the dog/ immediately/ showed his wild
 26 27
 joy/ on seeing his master/ as he thought he ought to be./

Thinking.—Two tests were selected which have been used in psychiatric practice in the study of schizophrenic and senile thinking disorders. The Kohs Block Test may be used to investigate the speed of forming a pattern, involving the ability to discriminate different forms and their spatial relations. The Hausmann absurdity test³ has been recommended for determination of schizophrenic thinking disorders.

1. Kohs Block Test: In our administration of this test, only the time score was used. For 66 patients, the corrected odd-even reliability coefficient was 0.96.

2. Hausmann's Test for Appreciation of Absurdities: This test was found to have practically zero reliability with 48 students. In a study on 24 psychiatric patients of above average intelligence and of ages varying from 18 to 45, the corrected odd-even reliability coefficient was found to be 0.57. In its present form the test is obviously valueless, but, as the low reliability is most likely related to the small number of units in the test, the test might be made useful by lengthening it.

INFLUENCE OF ANXIETY

The patients studied (all of whom were under treatment in the inpatient department of the Payne Whitney Clinic) were of superior intelligence. Their ages varied from 20 to 49. In all the patients anxiety was present in pathologic intensity, either as one of the most prominent symptoms, in the depressed patients, or as the outstanding symptom, in the psychoneurotic patients. The intensity of the anxiety

3. Muncie, W.: *Psychobiology and Psychiatry: A Textbook of Normal and Abnormal Human Behavior*, St. Louis, C. V. Mosby Company, 1939.

was estimated by subjective descriptions of anxiety and its physical accompaniments and by the observations on increases in pulse rate, sleep disorders, variations in food intake, increases in the fasting blood sugar and the leukocyte count⁴ and other psychopathologic phenomena attributable to anxiety. In 20 patients, adrenergic-cholinergic substances in the blood were determined in the evaluation of anxiety.⁵ Some of the psychologic tests which were discussed in the preceding pages were given when the patient experienced intense anxiety and were repeated when the anxiety had subsided. The minimal interval between test and retest was six weeks, but the period was usually two to three months and occasionally longer. With a considerable number of patients, a retest was not possible because they left the clinic before the time for retest had arrived, or at a time when testing was not possible for other reasons. A small group of 6 patients was studied when anxiety was greater at the time of the retest.

TABLE 1.—*Scores for Data on the Forward Digit Span Test*

	Mean		
	First Test (Intense Anxiety)	Second Test (Less Anxiety)	Critical Ratio * (D/s.e.diff.)
Longest span before error.....	6.0	6.9	2.6
Longest span before two consecutive errors.....	7.0	7.4	1.5
Longest span regardless of errors.....	7.1	7.6	1.9

* The critical ratio is the difference of the means divided by the standard error of the difference.

Attention.—(a) Directed Attention, Studied by the Digit Span: The forward digit span was given to a group of 35 patients who had intense anxiety at the time of the first test and whose anxiety had decreased at the time of the second test. When the results were scored for the number of errors before the last correct series, the mean score for forward repetition was 0.89 error and on the retest the mean score was 0.74 error. The critical ratio of the difference between these means does not approach statistical significance; so it must be said that a change in the clinical picture of the patient was not accompanied with a change in the results of the test when scored this way.

Table 1 gives the results of this test when it is scored in the three more conventional ways and when results obtained under the influence of different degrees of anxiety are compared. The critical ratio of the

4. Milhorat, A. T.; Small, S. M., and Diethelm, O.: Leukocytosis During Various Emotional States, *Arch. Neurol. & Psychiat.* **47**:779-792 (May) 1942.

5. Diethelm, O.; Doty, E. J., and Milhorat, A. T.: Emotions and Adrenergic and Cholinergic Changes in the Blood, *Arch. Neurol. & Psychiat.* **54**:110-115 (Aug.) 1945.

difference between the means on test and retest, when scored in terms of the longest span repeated before any error is made, approaches statistical significance, and it is therefore possible that a decrease in anxiety has operated to improve this score.

The reversed digit span was scored in the same ways. The mean number of errors before the longest possible span on the first test was 0.94 and that on the retest 0.83. This difference, of course, is not statistically significant.

Table 2 gives the data for the reversed digits scored in the more conventional manner.

These results are at odds with clinical experience, and the absence of a significant increase of the second score over the first is especially hard to explain when practice effect should operate in this direction also.

These data suggest that anxiety decreases active attention as measured by the longest span of attention before the error is made. No

TABLE 2.—*Scores for Data on the Reversed Digits Span Test*

	Mean		
	First Test (Intense Anxiety)	Second Test (Less Anxiety)	Critical Ratio (D/s.e.diff.)
Longest span before error.....	5.0	5.6	1.9
Longest span before two consecutive errors.....	6.1	6.5	1.2
Longest span regardless of errors.....	6.3	6.6	1.0

statistically significant changes were found when the digit span was scored by the longest span before two consecutive errors or by the longest span regardless of errors. The reversed digit span was not affected significantly by anxiety.

(b) Passive Attention, Studied by the "Barn Story": Forty-seven students recalled a mean number of 9.1 units in this story immediately after it was read. Fifty-four patients who revealed definite signs of anxiety at the time of the test obtained a mean score of 6.5 units. The critical ratio of the difference between these means is 2.24, thus indicating that the probability that this represents a real difference is better than 99 in 100. The students' scores showed greater variability, as indicated by a standard deviation of 6.2 and a range of 0 to 26, whereas the patients' distribution had a standard deviation of 5.5 and a range of 0 to 16. The greater variability in the distribution of students' scores is in part at least attributable to the concentration of patients' scores at the lower limit of the range. These results must be interpreted cautiously, since the two groups were unmatched on several variables which could conceivably contribute to the difference between the mean

scores. However, there is some indication that anxiety may have been a factor in reducing scores in view of the fact that 17 patients who showed pronounced anxiety all scored between 0 and 5.

Learning (studied by means of the maze test).—With 57 patients it was possible to study learning in a repeat test when anxiety had subsided.

Since a control test showed no reliable decrease in mean scores on a second maze test over a comparable period, these results indicate that learning is reliably slower in the presence of anxiety. Notable changes were observed in all three fields—error, trials and time—but not always concurrently. The extreme variation for 1 patient was from 154 errors, 28 trials and 1,665 seconds with intense anxiety to 66 errors, 19 trials and 742 seconds in the retest when anxiety was mild. The most extreme variation in errors was from 180 to 47; in trials, from 32 to 2, and in time, from 1,943 to 161 seconds. On the whole, the most pronounced improvement in all three factors

TABLE 3.—*Scores for Data on Learning in Retest*

	Mean		
	First Test (Intense Anxiety)	Second Test (Less Anxiety)	Critical Ratio (D/s.e.diff.)
Errors.....	109.7	75.1	2.9
Trials.....	20.5	14.2	3.1
Time, sec.....	1,541.9	960.2	3.9

was observed in patients who experienced intense anxiety during the first test and little anxiety during the repeat test. It is impossible to state whether any one of these three factors was affected more frequently or more markedly than the others. With 3 patients, anxiety was greater at the time of the retest than on the first test. This anxiety subsided the same day. With these 3 patients learning was affected adversely. For 2 of the patients the time for learning the test was increased; the third patient, on the other hand, showed a significant increase in trials, whereas the errors and time had decreased significantly. In 1 patient, an insecure person with high standards, anxiety became stirred up during the test when he made several errors in the beginning, and the total results were considerably less good than in the first test, although his intense anxiety had subsided greatly during the course of his illness.

Eleven patients failed to learn the maze. For 7 of these patients the learning scores were above the mean when their intense anxiety had subsided. For the remaining 4 patients learning scores were below the mean at a time when they still experienced considerable anxiety.

The findings on the maze test suggest that learning is slower in the presence of anxiety.

Retention (studied by means of the maze test).—Retention ability was tested by repeating the maze twenty-four hours after it was learned on each of two occasions, once when the patient revealed much anxiety and later, on the second maze, when anxiety was reduced.

Fifty-seven patients learned the maze at the first attempt. Table 4 gives the mean number of errors, trials and seconds required to relearn the maze twenty-four hours after the original learning.

When anxiety was greater, the number of trials was significantly greater. The extremes observed were 21 trials, under intense anxiety in the first test, and 6 trials, without anxiety in the retest four months later. A difference of 10 to 12 trials was frequent under the influence of anxiety. In 3 patients anxiety had increased at the time of the retest. This anxiety was only transient, lasting a few hours on the day of the test for retention, but was sufficient to affect retention unfavorably. For

TABLE 4.—Data on Relearning the Maze Test

	Mean		Critical Ratio (D/s.e.diff.)
	Relearning with Intense Anxiety	Relearning with Less Anxiety	
Errors.....	16.9	8.8	1.9
Trials.....	6.0	3.0	3.2
Time, sec.	280.9	158.8	2.4

2 of these patients the errors and the time increased markedly, whereas the number of trials increased less. For a third patient errors increased markedly, whereas the number of trials and the time decreased.

The findings suggest that retention ability is affected unfavorably by anxiety.

Thinking (studied by means of the Kohs Block Test).—To 64 patients, the Kohs Block Test was administered under conditions of extreme anxiety in the first test and less or no anxiety in the retest. The mean score for the first test was 90.2, and that for the retest, 110.6,⁶ giving a critical ratio of the difference of 4.2, representing probably a real improvement. (Experience in intelligence test batteries shows that the Kohs Block Test can be repeated after a short interval of time without appreciable practice effect.) The extremes observed were a score of 41, in the first test, and of 116, in the retest. For most patients the difference was from 20 to 40 points. For 18 patients the score was low, i. e., 8 to 73 in the first test. For 10 of these 18 patients there was an increase of 20 to 40 points in the retest without the influence

6. Higher scores are better in this test.

of anxiety; for 2 patients, an increase of 56 and 67 points, respectively, and for 6 patients, less than 20 points. For 8 patients, the first score was over 120 under the influence of anxiety, with an increase of only a few points without anxiety, i. e., a statistically insignificant change. For 6 patients the first score was over 120, and there was a notable increase (11 to 14 points) with lessened anxiety. For the majority of the patients (34), the test score under the influence of anxiety was between 75 and 120 and the increase under the influence of little or no anxiety was 12 to 38 points, 2 patients showing an increase of only 4 and 6 points, respectively, and 1 patient an increase of 45 points.

It seems that anxiety decreases the score significantly for most patients, but that there is a small group which is influenced little.

EVALUATION OF ANXIETY IN PSYCHIATRIC EXAMINATION

The standard psychiatric examination which has been developed in American psychiatry during the last forty years represents an attempt at objective determination of psychopathologic phenomena. Some of the tests discussed in the preceding pages are used in psychiatric examination, but what is to be studied through them is frequently not recognized by the physician. A brief review of the meaning of a psychiatric examination therefore seems indicated. It is also hoped that a clinically acceptable standardization of the present type of psychiatric examination will evolve.

Under "appearance and behavior" are noted findings which are indicative of the type of rapport, the patient's spontaneous and reactive behavior, motility disorders, dissociation and personality disorganization. The "characteristics of talk" reveal disorders of thinking and of symbolization, a tendency to substitution and dissociation. The observations noted under "emotional state and reactions" permit the physician to recognize various emotional disorders and the psychopathologic significance of any emotion present. Under "special preoccupations and experiences," or "topical material" or "content," as it is also called, dynamic factors can be seen, either directly or in the form of projections. It can be judged whether these findings are linked to intense emotional reactions and, if so, whether the emotions are largely dependent on the preoccupations or, on the contrary, cause them. "Orientation" is indicative of the clearness of consciousness and grasp, their disturbance being primarily due to toxic and organic factors and less frequently to psychodynamic factors or intense emotions. Under "Memory," recall of experiences in the remote and recent past and of immediate impressions are tested, and disorders in this field are indicative of cortical disturbance. These disorders may be of permanent nature, as in the "organic" psychoses, or transient, as in the various types of delirious disorders and

in severe disorders of thinking of the affective and schizophrenic types. Memory disorders may occur to a less extent under various emotional influences. Tests of recall of immediate impressions (repetition of three nonrelated words and recall after three minutes) and of general grasp and recall of a story which the patient has read aloud ("Cowboy Story") demonstrate readily the presence of confabulation. (Contrary to the general assumption, there is no test in the psychiatric examination to evaluate retention directly.) The "span of attention" is investigated by immediate repetition of digits, starting with three digits and increasing until the first failure. An additional test may be given in which the patient is requested to repeat the digits in reverse order. The simple "concentration test" of serial subtraction of 7 from 100 is valuable clinically. Intense emotions affect attention and concentration and, to a less extent, general grasp and recall. "General intellectual evaluation" (i. e., rough evaluation of general information, calculation, reasoning and judgment) is studied for the recognition of disorders of intellectual functions which may be due primarily to cortical damage, acquired prenatally, early or late in life, or to sweeping affective disorders, special preoccupations and thinking disorders. Failure in calculation may be due to general intellectual defects, thinking and attention disorders and to fatigue. Judgment is affected in any of the aforementioned disorders and under catathymic influences. "Insight" indicates the patient's awareness of his being ill, of the character of his illness and of the special dynamic factors involved.

This study was undertaken especially to gain an understanding of the influence of anxiety on psychologic functions. It demonstrates that anxiety affects attention, concentration, learning, retention and, to some extent, thinking. In any psychiatric examination one should always evaluate the influence of anxiety. It may be possible to gage the intensity of this emotion from the findings in the psychiatric examination. Unusual findings in the realm of the functions indicated should prompt the examiner to look for emotional factors. A psychiatric examination is therefore valuable in any evaluation of emotions in whatever psychologic or psychopathologic setting they occur, i. e., whether the disturbance is considered psychoneurotic, psychotic or psychosomatic. (It should be stressed that it is undesirable to use the term "psychotic," which does not connote a contrast to "psychoneurotic" and is a generalization which is as inaccurate as the older term "insane.")

It is to be expected that emotions other than anxiety affect various psychologic functions. Anxiety was selected because combined physiologic-psychopathologic studies have demonstrated the influence of this emotion on physiologic functions. Our findings, therefore, permit an objective evaluation of anxiety. Similar evaluation is at present possible with regard to tension, fear and resentment, whereas the emotions of

depression and mild elation do not seem to influence the physiologic functions studied. In the field of psychopathology, the depressive emotions have been credited with far reaching effects. It is most questionable whether depressive emotions cause severe thinking disorders of the type of confusion and memory and retention difficulties. It is more likely that anxiety, which seems to be present in every pathologic depressive reaction, causes these disorders. The effects of the depressive emotions can be established only when it becomes possible to study them without the presence of anxiety. A similar difficulty arises in the study of psychopathologic elation. In a study on the measurement of hyper-associative activity during elation,⁷ it was possible to demonstrate increased speed of thinking under the influence of elation. Some of the patients in this study did not give an indication of the presence of anxiety. No patient who suffered from intense anxiety without elation showed increased speed of thinking. The conclusion, therefore, seems warranted that elation was the essential factor. On the other hand, it is uncertain whether anxiety is not a contributory, or even a necessary, factor in pathologic elation.

A psychiatric examination presents a group of experiments which cannot be evaluated independently of each other. In every experiment the attitude of the subject to the situation is of great importance. In the study of maze learning, anxiety with respect to the test interfered greatly with learning, and the anxiety resulting from difficulty in learning affected retention. This anxiety could affect other tests which might be given immediately after the maze test. The same reaction may occur during a psychiatric examination. Anxiety which had not been very active before the examination may become intense with the questioning, and may increase or decrease during the further progress of the test.

SUMMARY

A group of tests were selected for the study of active and passive attention, learning, retention, immediate memory and thinking. The reliability was established in all tests which were used in this study.

Anxiety appears to decrease active attention, as measured by the longest span of digits before an error is made. Passive attention, as studied by the recall of the number of units of the "Barn Story," was affected adversely by intense anxiety. This effect was less clear when anxiety was not intense. Learning on the maze test was reliably slower in the presence of anxiety. Retention ability, tested by repetition of the maze test twenty-four hours after it was learned, was affected unfavorably by anxiety. Thinking was studied by means of the Kohs Block

7. Welch, L.; Diethelm, O., and Long, L.: Measurement of Hyper-Associative Activity During Elation, *J. Psychol.* **21**:113-126 (Jan.) 1946.

Test. It seems that anxiety decreases the score significantly with most patients, but there is a small group which is influenced little. The influence of anxiety in the different experiments was not uniform. It may happen that one or the other of the aforesaid functions is affected little, whereas all or the majority of the remaining functions are affected to a pronounced degree.

The possible influence of anxiety on the various functions which are tested in the current type of psychiatric examination has to be considered more seriously than has been done heretofore. It may be possible to gage the intensity of anxiety from the findings. It is necessary, however, that the technic of the examination be refined by a careful scoring of the "Cowboy Story" test and by the inclusion of additional tests which have been found useful and reliable in psychologic study.

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EFFECT OF QUINACRINE (ATABRINE) ON THE CENTRAL NERVOUS SYSTEM

Clinical and Electroencephalographic Studies

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CINCINNATI

THE INTRODUCTION of quinacrine hydrochloride (atabrine dihydrochloride) as an antimalarial agent has brought with it the usual problem of untoward reactions with which physicians must become familiar. Important among the toxic effects encountered have been psychotic reactions. The appearance of such reactions during the widespread use of this drug in the armed forces, as well as indications that some of the related antimalarial compounds being studied might also have an effect on the central nervous system, led to a request by the Board for the Coordination of Malarial Studies that we investigate this action of the drug in human subjects. The results of this study were transmitted to the Board in the summer of 1944.

Gaskill and Fitz-Hugh¹ recently reported on the incidence of such "toxic psychoses" among patients with malaria who had been treated with quinacrine. In seven months' experience in an army hospital in a highly endemic area, to which 7,604 patients with malaria were admitted, these authors encountered 35 persons in whom a "toxic psychosis" developed, an incidence of 0.4 per cent. The time of onset of the reaction varied from the third day of administration of quinacrine to twelve days after the last dose of the drug, the most common date of onset being the sixth day after completion of the therapy, the usual total dose of the drug being 2.1 Gm. Since the onset of the psychosis

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1. Gaskill, H. S., and Fitz-Hugh, T., Jr.: Toxic Psychoses Following Atabrine, Bull. U. S. Army M. Dept., 1945, no. 86, p. 63.

was often insidious, the authors stated the opinion that more careful observation might have disclosed an earlier date of onset. They described two types of responses: The first was characterized by sudden increase in motor and psychomotor activity, frequently accompanied with auditory and visual hallucinations, delusions and ideas of references, and an affect of euphoria and expansiveness. The second type began more insidiously with gradual clouding of the sensorium, disorientation, loss of memory for recent events and diminution of activity in both the intellectual and the motor sphere, with a predominant affect of bewilderment and fearfulness. The authors pointed out that the symptoms were apparently colored in part by the prepsychotic personality of the individual patient.

This excellent clinical report leaves unanswered several important questions. While the late onset of the reactions is strong presumptive evidence that they were induced by the quinacrine, the role of the pre-existing malarial infection together with the fatigue, undernutrition, dehydration, previous combat experience and other factors that might be expected among this group of patients is difficult to evaluate. The authors attempted to test this point by administering a second course of quinacrine to 16 of the patients who had recovered from a psychosis. Two of the patients received the drug because of a recurrence of malaria. Each patient received 0.2 Gm. of quinacrine hydrochloride every six hours for five doses, followed by 0.1 Gm. three times daily for six days, making a total of 2.8 Gm. Only 1 subject exhibited any untoward reaction. This patient became mildly excited on the last day the drug was administered, recovering completely in forty-eight hours. From these results the authors suggested the following alternative hypotheses:

... There is no specific causal relationship between atabrine and these psychoses; these toxic psychoses represent an unusual sensitivity reaction to atabrine in which at least temporary desensitization is produced by the attack; or this psychosis is a complex-conditioned sensitivity in which atabrine is one of several factors which must coincide in a given individual in order to produce this syndrome.

The influence of some of these complicating factors can be eliminated by studying the effects of quinacrine on normal healthy adults. Previous studies of delirium, both as experienced spontaneously in the course of various diseases² and as induced experimentally by anoxia,³ hypo-

2. (a) Romano, J., and Engel, G. L.: Delirium: I. Electroencephalographic Data, *Arch. Neurol. & Psychiat.* **51**:356 (April) 1944. (b) Engel, G. L., and Romano, J.: Delirium: II. Reversibility of the Electroencephalogram with Experimental Procedures, *ibid.* **51**:378 (April) 1944.

3. Engel, G. L.; Webb, J. P., and Ferris, E. B.: Quantitative Electroencephalographic Studies of Anoxia in Humans: Comparison with Acute Alcoholic Intoxication and Hypoglycemia, *J. Clin. Investigation* **24**:691, 1945.

glycemia³ and the administration of alcohol⁴ and other toxic materials,⁵ have yielded a technic ideally suited to this purpose. In these studies it was found that the electroencephalogram provided a sensitive indicator of changes in the physiologic status of the cortex under the circumstances previously cited. With the use of a quantitative method of analysis of frequency distribution in the electroencephalogram,⁶ it proved possible to correlate the level of consciousness with changes in frequency distribution. In general, reduction in the level of awareness was found to be associated with a shift toward slower frequency ranges; in the more extreme cases this was accompanied with a notable disruption of synchrony, as evidenced by the appearance of low voltage fast activity. Studies of the behavior of the patients and of the experimental subjects revealed that the basic psychologic disturbance in delirium is a reduction and an increased fluctuation in the level of awareness, and that the intellectual, emotional and motor behavior of these persons may best be understood in terms of a release of less well integrated or more primitive behavior resulting from reduction of higher cortical control.

It seemed likely from these earlier studies that if quinacrine, in reasonable dosage, exerted any influence on the cerebral cortex of normal human subjects, it should be possible with this electroencephalographic technic to detect such an effect even before clinical changes were apparent. Pick and Hunter⁷ reported changes in the electroencephalograms of cats under pentobarbital anesthesia and of pithed frogs during the administration of quinacrine. These observers noted the disappearance of fast activity and the development of slow waves of low amplitude. The dosage and the blood levels of quinacrine, however, were very high.

DESIGN OF EXPERIMENT

Five normal men, aged 26, 29, 30, 35 and 39, received quinacrine hydrochloride. A sixth subject, a man aged 30, served as a control. He received no quinacrine and was studied simultaneously with the experimental subjects. During a control

4. (a) Engel, G. L., and Rosenbaum, M.: Delirium: III. The Electroencephalographic Changes Associated with Acute Alcoholic Intoxication, *Arch. Neurol. & Psychiat.* **53**:44 (Jan.) 1945. (b) Engel, Webb and Ferris.³

5. Engel, G. L.; Romano, J., and Goldman, L.: Delirium: IV. Quantitative Electroencephalographic Study of a Case of Acute Arsenical Encephalopathy, *Arch. Neurol. & Psychiat.* **56**:659 (Dec.) 1947.

6. Engel, G. L.; Romano, J.; Ferris, E. B.; Webb, J. P., and Stevens, C. D.: A Simple Method of Determining Frequency Spectrums in the Electroencephalogram: Observations on the Effects of Physiological Variations in Dextrose, Oxygen, Posture and Acid-Base Balance on Normal Electroencephalogram, *Arch. Neurol. & Psychiat.* **51**:134 (Feb.) 1944.

7. Pick, E. P., and Hunter, J.: The Action of Atabrine on the Electro-cortico Potentials, *J. Pharmacol. & Exper. Therap.* **80**:354, 1944.

period of five to six days, all the subjects had electroencephalographic recordings twice daily, morning and afternoon, with simultaneous determinations of the blood sugar. During this period physical and neurologic examinations were carried out, and subjective and objective data on behavior were noted daily. Each of the 5 experimental subjects was then given 0.2 Gm. of quinacrine hydrochloride every four hours for the first twenty-four hours (total, 1.2 Gm.) and a total of 0.2 to 1.2 Gm. daily (in divided doses every four to eight hours) until the plasma level of the drug exceeded 100 micrograms per liter or until severity of symptoms necessitated discontinuance of administration of the drug or reduction of the dose. The daily doses for each subject are indicated in charts 1 to 5. It will be noted that plasma levels of 100 micrograms per liter or higher were obtained within six to ten days in 4 subjects and that the fifth subject discontinued taking the drug on the third day (plasma level of quinacrine, 75 micrograms per liter) because of the severe symptoms. No subject received quinacrine longer than ten days. During the period of administration of the drug simultaneous electroencephalographic recordings and determinations of the blood sugar, the plasma level of quinacrine and the rectal temperature (starting on the sixth day) were made twice daily, and subjective and objective data on behavior were noted. Similar observations were carried out until the twentieth day after administration of the drug had been initiated (ten to seventeen days after it had been discontinued). During the last six days observations were made only once daily. After a lapse of fifty-three days, to permit excretion of the drug, the subjects were observed twice daily for a third period, of four days. The control subject was studied simultaneously.

A three channel electroencephalograph, constructed by Mr. Albert Grass, was utilized in these experiments. Bipolar fronto-occipital tracings were obtained. A quantitative method of frequency analysis, described in detail elsewhere,⁸ was employed. Briefly, this involved counting the number of waves per second interval for a two hundred second strip and determining the percentile distribution of each wave frequency, which could then be expressed as a spectrum. From this, the mean frequency could be calculated by taking the arithmetical mean of the frequencies represented. The mean frequency yielded an adequate index of the shifts in frequency under the conditions of these experiments. For brevity's sake, the more extensive and space-consuming spectrums are omitted here except for a single illustrative sample (chart 6). All subjects had control electroencephalograms with over 95 per cent well developed alpha activity. Since the accuracy of the method is far greater in such circumstances, and since it is difficult or impossible to derive a mean frequency if the record contains much uncountable low voltage fast activity, subjects with good alpha rhythm were intentionally selected. Three of the subjects had had many previous electroencephalograms during the past two years, and the mean frequencies for these subjects had shown little fluctuation over that period. The range of daily variation in mean frequencies (for each subject) in the control period is illustrated in charts 1 to 5. The reliability and validity of this method are discussed in more detail in the references previously cited.⁹

The plasma levels of quinacrine were determined by the Masen method¹⁰ under the direction of Dr. Leon Schmidt, Christ Hospital, Cincinnati.

8. Engel, Webb and Ferris.³ Engel and others.⁶

9. Engel and Romano.² Engel, Webb and Ferris.³ Engel and Rosenbaum.^{4a} Engel, Romano and Goldman.⁵ Engel and others.⁶

10. Masen, J. M.: Quantitative Determination of Atabrine in Blood and Urine, *J. Biol. Chem.* **148**:529, 1943.

RESULTS

The individual data on each subject are graphically recorded (charts 1 to 5).

It will be noted from inspection of these charts that all subjects showed a sustained acceleration in frequency of the brain waves, beginning by the third or fourth day of administration of the drug and persisting for six to eight days after it had been discontinued. This increase in frequency was of pronounced degree in the records of 2 subjects, in which it was readily apparent on inspection alone (chart 6), and of moderate degree in the tracings of the remaining 3 subjects. Simultaneous measurements of the blood sugar and the rectal temperature failed to reveal any consistent trend which would account for this change in frequency of the brain waves. While no precise correlations with plasma levels of quinacrine are possible, in all instances the acceleration in frequency of brain waves appeared to be present when plasma levels of the drug exceeded 30 to 40 micrograms per liter. Since electroencephalograms and plasma levels of quinacrine were not obtained during the first two days of administration of the drug, the establishment of this effect at a lower plasma level cannot be ruled out. During the final period, after a lapse of fifty-three days, the mean frequencies were similar to those in the control period and the plasma levels of quinacrine were between 0 and 5 micrograms per liter. The electroencephalogram of the control subject showed no significant change during the course of the experiment.

Concurrently with the acceleration of the brain waves, certain psychologic symptoms appeared. All the subjects experienced some degree of motor restlessness, sleeplessness and awakening dreams, which at times were of frightening and nightmarish quality. The subjects showed psychologic acceleration and an unusual push of activity, and each subject was able to carry on more than ten to twelve hours of daily activity in the hospital and medical school. This was associated with varying amounts of tension, irritability and anxiety. In 1 subject (subject 1) this reached on the ninth day the magnitude of an acute panic reaction, with considerable flight of ideas and anxiety, and required hospitalization. This case so well characterizes the nature of the reaction that it is reported in detail.

SUBJECT 1 (chart 1).—A man aged 39, in good health, had had fourteen control electroencephalograms taken during the preceding two years. Psychologic tests of awareness had also been administered repeatedly in the course of other studies during this period. During the five days preceding the administration of quinacrine, records were taken twice daily, the mean frequency ranging from 9.07 to 9.20 per second. In the total of 24 control records during two years the highest mean frequency was 9.22 per second.

On completion of the control period, 0.2 Gm. of quinacrine hydrochloride was taken every four hours, a total of 1.2 Gm. in the first twenty-four hours, and 0.1 Gm. three times a day for the next two days. On the second day he noted slight epigastric distress and mild diarrhea. At the end of the third day the plasma level of quinacrine was 30 micrograms per liter and the mean electroencephalographic frequency was 9.59 per second. On the fourth and fifth days he took 0.2 Gm. of quinacrine hydrochloride three times daily. Mild gastrointestinal symptoms continued, and the development of pigmentation was noted. Sleep was fitful. The plasma level of quinacrine reached 55 micrograms per liter, and the mean electroencephalographic frequency was 10.25 per second. On the sixth day a total of 1.2 Gm. of the drug was taken, and the plasma level of the drug was 83 micrograms per

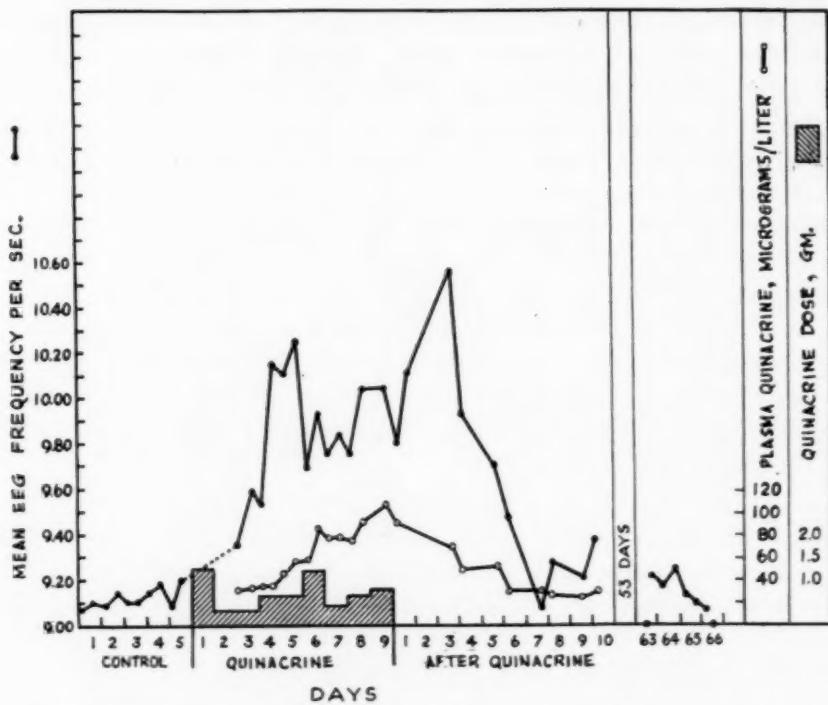


Chart 1 (subject 1).—Mean electroencephalographic frequencies and plasma levels of quinacrine during administration of the drug.

liter. That night he had difficulty in getting to sleep and slept fitfully. He awoke many times and had many unremembered dreams, which awakened him. The next two days (seventh and eighth) he took 0.4 and 0.6 Gm. daily, respectively, and the plasma level of the quinacrine reached 105 micrograms per liter. The mean electroencephalographic frequency fluctuated but continued to be accelerated. The symptoms continued; in addition, he noted weakness, general malaise, chilliness, sweating and aching of the extremities. The rectal temperature was 100 F. Dreams of nightmarish quality awakened him frequently. The next day he took 0.7 Gm. of the drug. That night he retired at 9 p. m. but was unable to sleep. He felt very restless and was bombarded with thoughts. He had difficulty in manipulating

the alarm clock, which rang at 11 p. m. He tried to reset it but was unable to see the alarm hand clearly. He tried to read but was too distracted by extraneous thoughts and ideas flashing into his mind. Problems seemed at first easy of solution but then became jumbled, and a montage effect was attained. He tried to write a letter but made errors and was distracted. He turned out the lights, but in the darkness the symptoms grew worse; he began to feel progressively more frightened and panicky and finally called for help. A sample of blood was drawn, yielding a plasma level of 105 micrograms of quinacrine per liter. Sodium amytal, 0.1 Gm., was administered, after which the symptoms abated somewhat and he was able to sleep. The following morning he was somewhat euphoric and joked about his experience of the previous night. However, shortly he again began to feel panicky and harassed and then depressed. Examination of the level of consciousness at this point revealed that there was no reduction of awareness; indeed, there appeared to be a heightening of awareness and an actual acceleration of mental activity. The mean electroencephalographic frequency was 10.10 per second.

The patient was hospitalized and given sodium amytal by mouth and 5 per cent dextrose in distilled water by vein. Administration of quinacrine was discontinued. The symptoms rapidly subsided and within twenty-four hours had largely disappeared. The acceleration in the mean electroencephalographic frequency continued for two days and then rapidly decreased. The plasma level of the quinacrine decreased slowly, reaching 30 micrograms per liter in ten days.

COMMENT

Initially, this reaction was interpreted as a delirium, but further scrutiny revealed that the level of consciousness was not reduced and that attention was not impaired. The subject was apparently so bombarded by stimuli that he was unable to cope with them. The apparent confusion was probably due to multiplicity of thoughts and concomitant anxiety.

Brief clinical notes on the behavior of the other subjects follow; the other data are presented graphically (charts 2 to 5).

SUBJECT 2 (chart 2).—The subject, aged 29, slept poorly and experienced a tired feeling in the legs. On the fifth day he had severe insomnia, which was unusual for him, as well as nausea, slight diarrhea, abdominal cramps, aching extremities, night sweats, chilliness, a rectal temperature of 101 to 103 F. and lassitude with restlessness. In spite of malaise and other symptoms, the subject noted a considerable push of activity and worked late at night. The maximum plasma level of the quinacrine was 102 micrograms per liter. Acceleration of the electroencephalographic frequency was striking (charts 2 and 6). The drug was discontinued on the seventh day, after which symptoms rapidly subsided.

SUBJECT 3 (chart 3).—The subject, aged 26, on the third day of administration of the drug began to note restlessness, fitful sleep and frequent awakening from bad dreams. There were mild abdominal cramps from time to time. Insomnia and anxiety dreams increased, and he had two attacks of migraine, with scintillating scotomas. On the ninth day he felt "almost euphoric" but was easily fatigued. He felt a tremendous pressure of activity and emotional lability. The drug was discontinued on the tenth day, and symptoms rapidly subsided. The maximum

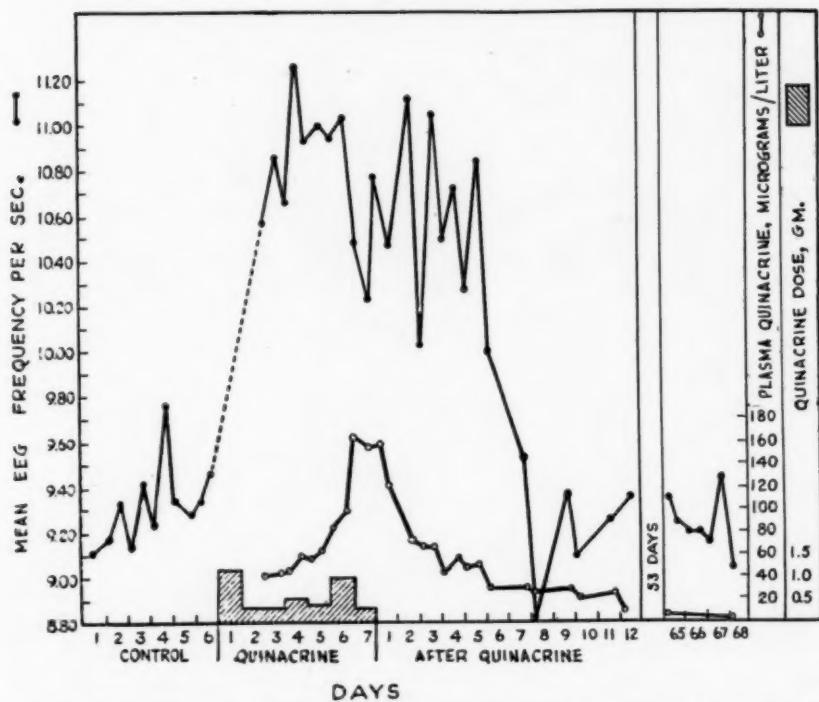


Chart 2 (subject 2).—Mean electroencephalographic frequencies and plasma levels of quinacrine during administration of the drug.

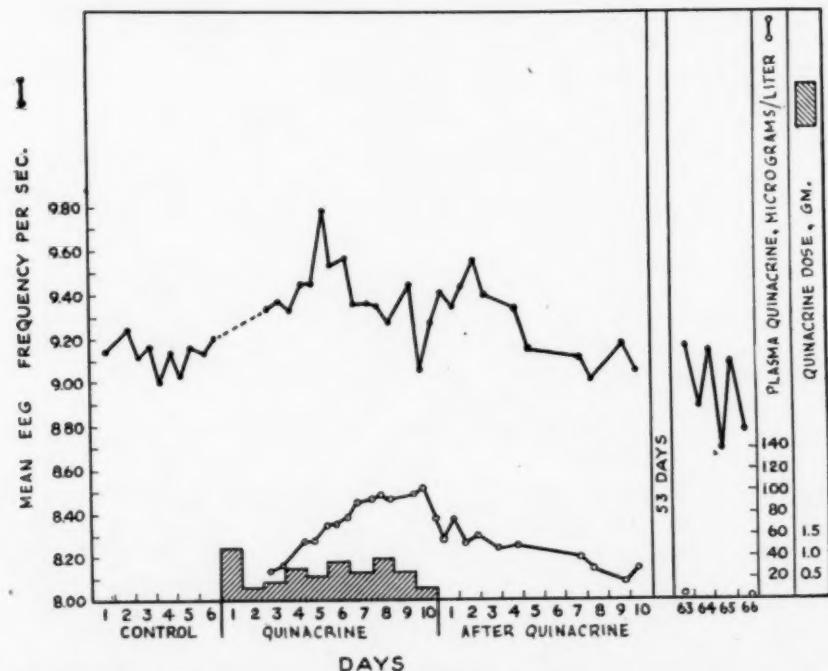


Chart 3 (subject 3).—Mean electroencephalographic frequencies and plasma levels of quinacrine during administration of the drug.

plasma level of the drug was 100 micrograms per liter, reached on the tenth day.

SUBJECT 4 (chart 4).—The subject, aged 35, had onset of intermittent abdominal cramps and diarrhea on the fifth day. On the seventh day sleep was disturbed by repeated terrifying dreams. He felt listless, tired and irritable but worked efficiently and under pressure. Anxiety dreams and broken sleep continued. On the tenth night he stayed awake almost all night and worked. The drug was discontinued, and these symptoms subsided over the course of the next four or five days. The maximum plasma level of quinacrine was 110 micrograms per liter, on the eighth day.

SUBJECT 5 (chart 5).—The subject, aged 29, received the drug only three days and asked that the experiment be discontinued because of unpleasant symptoms. Two days later furunculosis developed, for which he was hospitalized and treated successfully with penicillin. Symptoms during the period of quinacrine therapy consisted of malaise, headache and extreme lethargy.

Other clinical observations during the period of administration of the drug were as follows: All subjects experienced some degree of nausea, abdominal cramps and diarrhea. In all the subjects, gastrointestinal symptoms were relieved by food, and in spite of symptoms the appetite did not seem to be impaired. The body weight was measured in 1 subject (subject 4), who lost 7 pounds (3.2 Kg.) during the course of the experiment. It is probable that each subject lost some weight.

Chilly sensations, night sweats, heaviness of the legs and feet and occasional joint discomfort were experienced by 2 subjects. One of these (subject 2) had a rectal temperature of 101 to 103 F. on the seventh day, at the height of the clinical reaction. The plasma level of the drug was 162 micrograms per liter at this time, and the temperature fell to normal as soon as the drug was discontinued. Subject 5, who also had furunculosis, had a temperature of 100.8 F. three days after the drug had been discontinued; the temperatures of the remaining subjects did not exceed their maximum control levels by more than 0.5 F.

All subjects became deeply pigmented, and some pigmentation was still visible at the end of the experimental period (sixty-six days), even though the plasma level of the drug was zero at this time. The drug appeared to be excreted in the urine, feces, saliva and sweat. Two subjects noted itching. One subject (subject 4) noted the development of a lichen-like lesion on the anterior surface of the right leg, lasting about two months. Two subjects noted photophobia, and in 1 of these subjects episcleritis developed.

All the subjects agreed that the symptoms increased after each ingestion of the drug and diminished rapidly after discontinuance of the drug, even though the plasma level fell slowly. In general, the severer symptoms appeared to develop after the plasma level had reached 50 micrograms per liter.

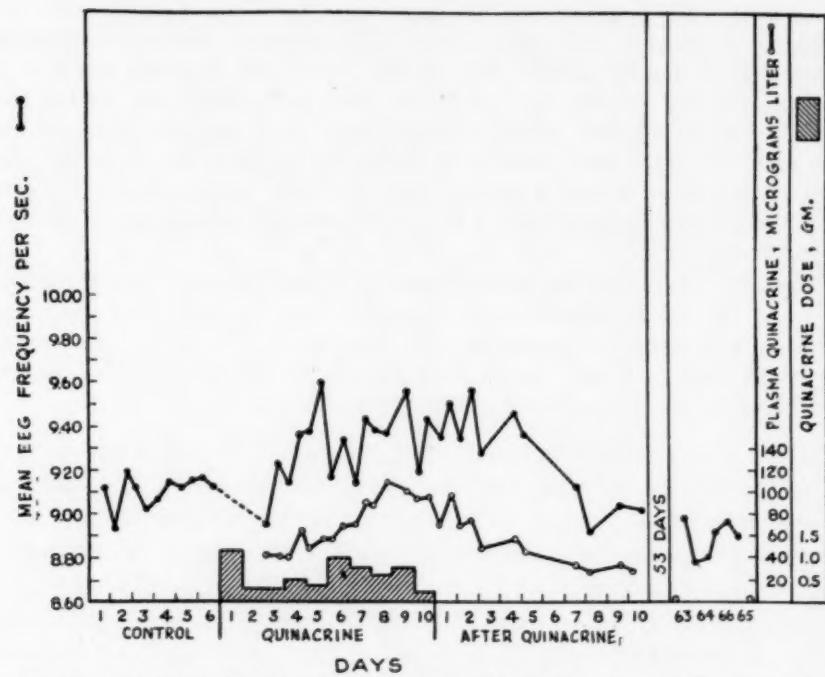


Chart 4 (subject 4).—Mean electroencephalographic frequencies and plasma levels of quinacrine during administration of the drug.

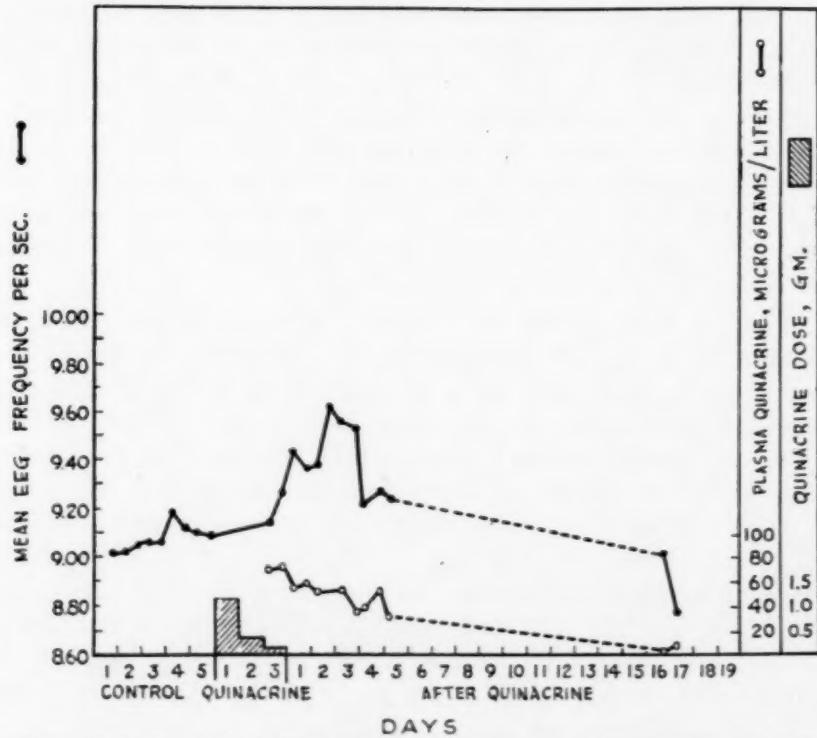


Chart 5 (subject 5).—Mean electroencephalographic frequencies and plasma levels of quinacrine during administration of the drug.

COMMENT

The clinical and electroencephalographic data obtained in this experiment constitute conclusive evidence that quinacrine acts as a stimulant to the central nervous system. The clinical symptoms included motor acceleration, restlessness, sleeplessness and increased capacity for work. Associated with this was an acceleration of the brain waves. Previous data have clearly established that, whereas depression of cortical activity

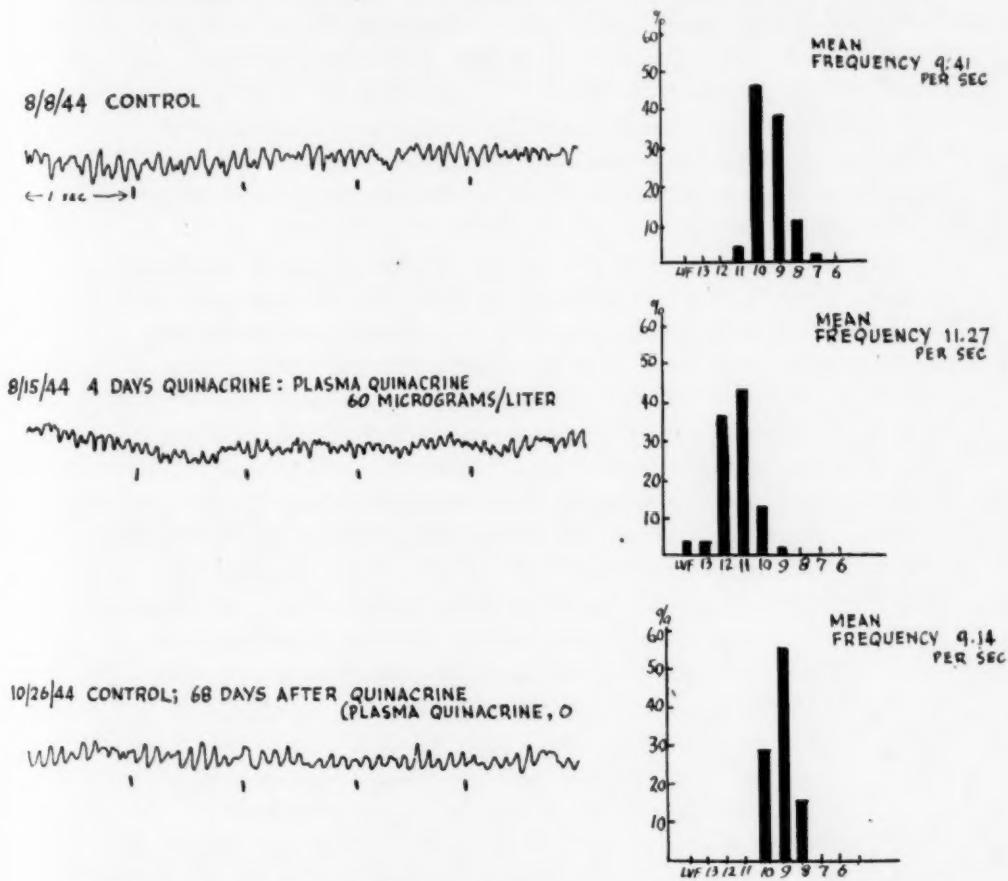


Chart 6 (subject 2).—Maximum electroencephalographic changes during administration of quinacrine hydrochloride.

is associated with slowing of the brain waves, known cortical stimulants (amphetamine, caffeine, epinephrine and camphor) produce acceleration of the brain waves.¹¹ The clinical manifestations noted in these subjects

11. Gibbs, F. G., and Maltby, G.: Effects on the Electrical Activity of the Cortex of Certain Depressant and Stimulant Drugs, *J. Pharmacol. & Exper. Therap.* **78**:1 1943. Engel and Romano.² Engel, Webb and Ferris.³ Engel and Rosenbaum.^{4a} Engel, Romano and Goldman.⁵

were quite similar to those noted in patients receiving excessive doses of amphetamine or caffeine.

These results were unexpected. Clinical reports we had received led us to anticipate that the toxic psychosis noted was a delirium, in which the basic disturbance was a reduction in the level of awareness. Indeed, the first interpretation of the reaction of subject 1 was that of delirium. But the evaluation of the level of awareness and the electroencephalographic findings failed to confirm this impression. Our anticipation of delirium as the type of reaction to be expected was so great that it was only at this point that we recognized how consistent had been the behavior of the other subjects, as recorded in their daily diary. The correlation with the obvious acceleration of the electroencephalographic frequencies then became clear. Efforts to correlate this electroencephalographic change with an increase in blood sugar or in body temperature proved unsuccessful.

When the dynamics of this reaction are analyzed, the confusion with delirium becomes understandable. In delirium the basic disturbance is a reduction in the level of consciousness. The consistent slowing of the brain waves associated with this reduction has been interpreted as probably related to reduction in cortical metabolism.¹² With this reduction in consciousness and impairment of cortical function, the patient becomes less able to deal with his external environment, on the one hand, and with certain instinctual drives, on the other. There is a falling back or regression to less well integrated behavior in the intellectual, emotional and motor spheres, with a release of more primitive types of behavior, usually with much accompanying anxiety. The reaction observed with quinacrine starts out on exactly the opposite basis. There are heightened awareness, increased activity and for a while, even increased efficiency, as has already been noted empirically with amphetamine. Beyond a certain point, however, the facilitation of the free flow of ideas becomes so great that the patient is unable to cope with this bombardment. Then psychologic decompensation is to be expected. The psychologic defenses are weakened, as they are in delirium, but by a different mechanism. Excitement, panic, increase in anxiety and aggressive behavior result. This was the stage reached in subject 1. Carried one step further, it seems reasonable that were this process to continue indefinitely, especially in a person with previous deprivations, the physiologic needs of the brain might be exceeded and decompensation at a physiologic level occur. The result would be reduced awareness and delirium. Thus, the two types of clinical pictures described by Gaskill and Fitz-Hugh might be explained.

12. Engel and Romano.² Engel, Webb and Ferris.^{3a} Engel and Rosenbaum.^{4a}

The results with these 5 subjects suggest that quinacrine uniformly acts as a cortical stimulant, although it is noteworthy that the degree of acceleration of the electroencephalographic frequency did not necessarily correlate with the magnitude of the symptoms. Undoubtedly, preexistent psychologic factors also play a role. However, all our subjects showed some toxic reaction to the drug, which has not been the experience of other observers with larger series and at comparable plasma levels of the drug.¹³ Shannon has suggested that our plasma levels of quinacrine may be too low through technical error. We were unable to check this point conclusively, although a determination of the quinacrine level in several specimens by both the Masen and the Brodie¹⁴ method gave identical results. In any event, the quantity of the drug administered to our subjects was considerably in excess of that recommended for treatment of the attack, which consists of 0.2 Gm. of quinacrine hydrochloride every six hours for five doses and then 0.1 Gm. three times a day for six days, a total of 2.8 Gm. of quinacrine hydrochloride in seven days. It is certainly justifiable to conclude that in those patients who show toxic symptoms, and certainly in those who show psychic symptoms, the drug acts as a cortical stimulant. The mechanism of this action of quinacrine on the central nervous system is not clarified by these experiments, but it is noteworthy that our results can be considered consistent with observations by Waelsch and Nachmansohn¹⁵ that quinacrine is a strong inhibitor of cholinesterase. With inhibition of brain cholinesterase fast activity in the electroencephalogram is to be expected.¹⁶ In this regard quinacrine has certain properties in common with diisopropylfluorophosphate (DFP), a powerful anticholinesterase, which also produces stimulant effects on the central nervous system and the electroencephalogram.

While no special attention was directed to the problem of therapy, it would seem that a cortical depressant would be indicated. Sodium amyta seemed effective in the 1 case in which it was tried.

SUMMARY

Clinical and electroencephalographic observations were made on 5 normal adults during the administration of quinacrine hydrochloride (atabrine dihydrochloride). The daily dose ranged from 0.2 to 1.2 Gm.

13. Shannon, J. A.: Personal communication to the authors.
14. Brodie, B. B., and Udenfried, S.: The Estimation of Atabrine in Biological Fluids and Tissues, *J. Biol. Chem.* **151**:299, 1943.
15. Waelsch, H., and Nachmansohn, D.: On the Toxicity of Atabrine, *Proc. Soc. Exper. Biol. & Med.* **54**:336, 1943.
16. Forster, F. M.: Action of Acetylcholine on Motor Cortex, *Arch. Neurol. & Psychiat.* **54**:391 (Nov.-Dec.) 1946.

until the plasma level exceeded 100 micrograms per liter or until the severity of symptoms led to discontinuation. The period of administration of the drug did not exceed ten days. In all cases evidence of pronounced psychologic stimulation occurred, and the electroencephalogram showed a significant shift toward faster frequencies. These manifestations appeared by the third day and persisted for six to eight days after the drug had been discontinued, and until the plasma level had fallen to less than 40 micrograms per liter.

These data constitute evidence that quinacrine acts as a cortical stimulant.

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Cincinnati General Hospital (Dr. Ferris).

VITAMIN E IN TREATMENT OF MENTAL DISORDERS

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AND

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EVIDENCE of a vitamin deficiency is usually considered a valid indication for the use of the vitamin as a therapeutic agent. No conclusive evidence of a deficiency of vitamin E has been presented in human beings. Nevertheless, this vitamin has been used in therapeutic tests and favorable results have been reported in cases of habitual abortion,¹ premature separation of the placenta,² chronic nephritis associated with hypertensive vascular disease³ and the menopausal syndrome.⁴

The advent of more potent, purified preparations has made possible intensification of research in a wider field of clinical application. Christy gave preparations of vitamin E to 25 patients with surgical menopause.

No patient was treated who did not complain of severe symptoms of vasomotor instability. The amount of the drug taken varied from 10 to 30 mg. [of ephynal acetate] a day . . . over periods of from one to six weeks. Seven patients reported complete and 16 great relief. . . . In some cases vitamin E seems more effective in relieving the symptoms of vasomotor instability than estrogens.^{4b}

The favorable results obtained by Christy in treatment of the menopause, a condition fraught with emotional disturbances ranging from neurotic complaints to frank psychotic manifestations, prompted us to test the effect of vitamin E in cases of mental disorders occurring in the involutional age period.

PRESENT STUDY

Material and Method.—Subjects were selected at random from inpatients with chronic mental disease. Later in the study patients with illnesses of recent origin and patients of a younger age group were included. Thus, a repre-

From the Butler Hospital.

1. The Vitamins: A Symposium, Chicago, American Medical Association, 1939, p. 595. Shute, E.: Vitamin E in Habitual Abortion and Habitual Miscarriage, *J. Obst. & Gynaec. Brit. Emp.* **49**:534-541, 1942.
2. Shute, E.: Vitamin E in the Prophylaxis of Abruptio Placentae, *Surg., Gynec. & Obst.* **75**:515-519, 1942.
3. Shute, E.: The Effect of Vitamin E upon Impaired Kidney Function, *Canad. M. A. J.* **52**:151-153, 1945.
4. Christy, C. J.: (a) Vitamin E in Menopause: Preliminary Report of Experimental and Clinical Study, *Am. J. Obst. & Gynec.* **50**:84-87, 1945; (b) abstracted, *J. A. M. A.* **129**:406 (Sept. 29) 1945.

Clinical Data on Patients with Mental Disorders Treated with a Preparation of Vitamin E

Case Number	Age, Years	Female Subjects	Diagnosis	Duration of Illness, Years	Menopause	Period of Tocopherol Therapy, Days*	Vaginal Smears §			Blood Pressure		
							Condition at End of First Course		Condition at End of Second Course	Before Treatment	During Treatment	At End of Treatment
							Medication	Cessation	Medication	Cessation	Medication	Cessation
1	46		Involutorial psychosis, melancholia	<1	No	13	++	++	++	++	120/70	130/80
2	61		Involutorial psychosis, melancholia	8	Yes	14	++	++	++	++	150/95	130/85
3	50		Involutorial psychosis, melancholia	1	Yes	69	0	0	0	0	115/70	105/65
4	72		Involutorial psychosis, melancholia	5	Yes	21	0	0	0	0
5	60		Dementia precoox, type undetermined	6	Yes	47	0	0	0	0
6	35		Dementia precoox, catatonic type	1	No	14	0	0	0	0	105/60	105/60
7	64		Dementia precoox, catatonic type	37	Yes	45	0	0	0	0
8	38		Dementia precoox, paranoid type	<1	Yes	20	0	0	0	0
9	35		Dementia precoox, catatonic type	1	No	20 ^a	0	0	0	0
10	36		Dementia precoox, mixed type	2	No	7	0	0	0	0	115/70	115/65
11	41		Dementia precoox, mixed type	<1	No	28	0	0	0	0
12	26		Dementia precoox, catatonic type	<1	No	21	0	0	0	0
13	52		Manic-depressive psychosis, mixed type	<1	Yes	8	0	0	0	0	100/60	100/60
14	78		Manic-depressive psychosis, mixed type	4	Yes	63	0	0	0	0
15	42		Psychosis with cerebral arteriosclerosis	1	Yes	8	0	0	0	0	105/65	90/60
16	66		Psychosis with cerebral arteriosclerosis	<1	Yes	9	0	0	0	0
17	60		Unclassified psychosis	5	Yes	14	0	0	0	0	100/75	150/80
18	36		Psychoneurosis; neuroasthenia; alcohol and drug addiction	1	No	36	0	0	0	0	115/75	115/65
19	79		Psychoneurosis; anxiety state	6	Yes	14	0	0	0	0	135/70	155/65
20	76		Psychoneurosis; anxiety state	3	Yes	13	0	0	0	0
21	46		Psychoneurosis; hypochondriasis	1	Yes	26	0	0	0	0	145/65	145/65
22	68		Psychosis with psychopathic reactions	15	Yes	14	0	0	0	0	140/70	180/70
23	66		Psychosis with psychopathic personality; hysterical and involutional reactions	1	Yes	26	0	0	0	0	135/80	140/70
24	52		Psychosis with psychopathic personality; pathologic emotionality, hypochondriasis	1	Yes	14	0	0	0	0
Male Subjects												
25	61		Involutorial psychosis, melancholia; early senile arteriosclerosis	15	52 ^a	0	0	0	0
26	73		Manic-depressive psychosis, depressed type	7	23 ^b	0	0	0	0
27	58		Manic-depressive psychosis, depressed type with cerebral arteriosclerosis	<1	8 ^b	0	0	0	0
28	65		Psychosis with cerebral arteriosclerosis	9	14 ^b	0	0	0	0
29	68		Psychosis with cerebral arteriosclerosis	5	17 ^b	0	0	0	0
30	63		Psychosis with cerebral arteriosclerosis	<1	18	0	0	0	0	145/50	140/50
31	63		Psychosis with cerebral arteriosclerosis	7	59 ^c	0	0	0	0
32	82		Psychosis with cerebral arteriosclerosis	4	14	0	0	0	0
33	67		Psychosis with cerebral arteriosclerosis	2	34 ^a	0	0	0	0	150/85	150/80
34	73		Senile psychosis, simple deterioration	10	79 ^b	0	0	0	0	170/80	140/70
35	65		Psychosis with disease of the brain, unspecified Pick's disease? Cerebral arteriosclerosis?	6	121 ^a	0	0	0	0

* All subjects received 50 mg. of a preparation of mixed tocopherols ("tofexin") daily except where indicated. In this column, a, means administration on alternate days; b, administration twice daily; c, administration of "ephynal acetate" 10 mg., three times a day, and e, administration of "ephynal acetate," 30 mg., twice daily.

† The indicated duration of the illness of less than one year.

sentative cross section of various mental disorders in hospitalized patients was obtained. A total of 35 patients were studied of whom 24 were women and 11 men. The duration of the illness of 16 patients was one year or less. Of these, 12 were experiencing their first mental illness. All subjects were studied in the controlled environment of the hospital.

The predominant pattern of medication was 1 capsule of a commercial preparation ("tofaxin") containing 50 mg. of mixed (alpha, beta and gamma) tocopherols, of which 30 mg. was alpha tocopherol,⁵ given over periods ranging from seven to one hundred and twenty-one days with various patients. In several instances, 1 capsule was given twice daily, or only on alternate days, to test the effect of different doses. "Ephynal acetate" (alpha tocopherol acetate) was used for several male patients in doses of 10 mg. three times daily. Estrogenic levels were determined in 7 female subjects before institution of treatment and after two weeks of medication with the vitamin E preparation by the vaginal smear method of Shorr⁶ and Salmon and Frank.⁷ On the basis of results obtained for the first few patients who underwent therapeutic tests with the vitamin E preparation, we included determinations of the blood pressure to test the possible association of increase in blood pressure with the observed increase in psychomotor activity resulting from the drug.

The diagnoses for the patients studied, their ages, the duration of their illness, the duration of medication and dosage employed and other facts pertaining to the method and results of study are assembled in the accompanying table.

Results.—Two patients (11 and 27 in the table) experienced a complete remission with administration of the preparation of tocopherols and were discharged home. One of these (27), relapsed in two weeks after discontinuation of treatment and returned to the hospital. While he benefited somewhat from a repetition of vitamin E medication, he experienced a complete and enduring remission from electric shock and a change in vocation.

Five patients (2, 4, 18, 31 and 33) showed definite improvement, not leading to complete remission or to discharge from the hospital. Interruption of medication of patients 2 and 18 resulted in a partial relapse. Resumption of the treatment over a prolonged period did not lead to further improvement, beyond that obtained in the first course of medication. The common features of the illnesses of the patients who showed improvement were depression, agitation and anxiety, with moderate confusion and blocking of speech.

Increased psychomotor activity during medication with tocopherols was observed in 14 patients. The change in 12 of these patients consisted in mere intensification of the patient's old symptoms, with no

5. "Tofaxin" was supplied by the Winthrop Chemical Company, Inc., through the courtesy of Mr. Shephard M. Crain.

6. Shorr, E.: New Technic for Staining Vaginal Smears: Single Differential Stain, *Science* **94**:545-546, 1941.

7. Salmon, U. J., and Frank, R. T.: Hormonal Factors Affecting Vaginal Smears in Castrates and After Menopause, *Proc. Soc. Exper. Biol. & Med.* **33**:612-614, 1936.

new symptoms. Two of these 14 patients (1 and 9) became definitely worse during medication with tocopherols, exhibiting new symptoms. Both patients were given the drug shortly after admission, in an acute phase of development of their illness; it is possible that their illness would have become worse regardless of medication. The net result of administration of tocopherols in this group of 14 patients was an aggravation of clinical behavior. The most prominent changes in behavior in these patients were an increase in somatic, neurotic or hypochondriacal complaints; a restless and interrupted pattern of sleep; increased agitation; an increased need to discuss personal problems, and, in 1 instance, assaultiveness. Owing to this form of undesirable stimulation, the planned minimum course of two weeks of medication with the vitamin E preparation was shortened in several cases.

In most instances in which the patient showed improvement or increased psychomotor activity, a change in behavior was noticeable after three or four doses (accumulated 150 to 200 mg.) of a vitamin E preparation. After discontinuation of medication, the increase in psychomotor activity abated within a few days, except for the 2 patients (1 and 9) described in the preceding paragraph, who continued to show a downward trend in their illness.

No appreciable change was observed in the remaining group of 14 patients (table).

Four patients (3, 8, 21 and 24) complained of menopausal symptoms of a vasomotor type. One of these (patient 3) reported complete relief from vasomotor symptoms; the remaining 3 patients had partial relief. None of these patients showed improvement in mental condition. The subject who was completely relieved of menopausal symptoms made a determined attempt at suicide on the forty-fifth day of continuous medication with tocopherols.

Estrogenic activity determined in 7 subjects by the vaginal smear method showed no appreciable change in 5 patients after two weeks of medication with tocopherols. A moderate decrease in estrogenic level was observed in 2 subjects.

Increase in blood pressure, anticipated on the basis of psychomotor activity in a number of patients, did not occur. A trend toward transitory reduction in both systolic and diastolic blood pressure was observed several days after beginning of medication with tocopherols in 3 patients with arteriosclerosis.

Five patients of this series subsequently recovered with other methods of treatment and left the hospital. Three patients (1, 3 and 27) had a satisfactory remission following electric convulsive treatment. One patient (8) recovered after ambulatory subshock insulin therapy, and 1 patient (21) showed a satisfactory remission with psychotherapy.

COMMENT

The conditions treated and the doses of concentrated preparations of tocopherols used in these studies indicate the possibility that the therapeutic effect is achieved not by correction of a deficiency of vitamin E, but, rather, by a pharmacodynamic effect beyond that of a catalytic function, usually ascribed to vitamin substances. The patients tested in these studies came from financially well endowed families and probably had received sufficient nourishment before admission to the hospital. While in the hospital, the patients received an adequate diet; in addition, many subjects of this study were receiving adequate doses of polyvitamin preparations before inception of and during the study. It may be assumed that they did not have a deficiency of the commonly known vitamins. To the best of present day knowledge, the menopausal symptoms of the patients of Christy,^{4a} which occurred after operative removal of the gonads, cannot be ascribed to a deficiency of vitamin E. We assume, therefore, that the beneficial effects of tocopherols in the menopausal syndrome and the effects observed in our patients are due not to correction of a vitamin deficiency, but, rather, to a drug effect of tocopherol.

The general effect of tocopherols in our patients seemed to be that of stimulation. The stimulative effect was observed in 60 per cent of our patients. The effect on behavior was evidently dissociated from the beneficial effect on the menopausal vasomotor disturbances in the few patients whom we were able to test. The results of discontinuation and resumption of the medication with tocopherols in 4 patients in whom we observed improvement lead us to believe that the improvement in their mental condition was associated with the administration of tocopherol. The obvious increase in psychomotor activity in 12 patients, several of whom had chronic illnesses and had been under observation over a considerable period, coincided remarkably with administration of tocopherols, an observation which, to us, again indicates that the vitamin E preparation was the cause of the change in behavior.

SUMMARY AND CONCLUSIONS

The vitamin E preparations (tocopherols) used in these studies had a perceptible influence on psychomotor activity of mentally ill patients in 60 per cent of the cases studied. The observed effect was of the nature of stimulation, resulting in clinical improvement in 20 per cent of the subjects and in clinical intensification of symptoms in 40 per cent. No appreciable change in behavior was observed in the rest. The beneficial results were most obvious in patients whose illness was characterized chiefly by depression, agitation, anxiety and decreased ability for verbalization.

The number of complete remissions following medication with tocopherols was not significantly greater than that of the expected spontaneous remissions.

The value of tocopherol (vitamin E) as a therapeutic agent in cases of mental disorders ranks below that of accepted shock treatments. Preparations of vitamin E, however, may have some value in the conservative management of depressed mental patients for whom shock therapy is contraindicated.

The described effects of vitamin E therapy are considered to be due to a drug effect of tocopherol rather than to correction of a deficiency of vitamin E.

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SODIUM AMYTAL IN TREATMENT OF APHASIA

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WHILE on military duty in North Africa in 1943, Stein and I had the opportunity to observe the effects of intravenous administration of sodium amytal on a group of patients with dysphasia following shell fragment wounds of the dominant cerebral hemisphere. It was found that motor aphasia improved suddenly and dramatically in response to this medication. It was observed, too, that in some cases this improvement was sustained long after the effects of the sodium amytal had worn off. Furthermore, during the period of work with the patient, the helpless frustration reactions so commonly observed in aphasic patients did not appear and the patient was capable of sustained effort far beyond that which he showed without the drug. For these reasons, it was felt that the drug would be useful in the rehabilitation of soldiers with aphasia due to cerebral injuries. These observations have been verified by other investigators; in some cases the drug has had the anticipated beneficial effect.

Since returning to civilian practice, I have been able to demonstrate the usefulness of this drug. Since the civilian physician has relatively little contact with military medical literature, a brief note bringing the matter to the attention of a wider circle of medical readers seemed advisable. The following 2 cases illustrate the effects of sodium amytal in aphasia.

REPORT OF CASES

CASE 1.—R. H., a woman aged 40, experienced right hemiplegia associated with mixed aphasia after operation for a meningioma involving the left temporo-parietal region. She responded to her aphasia with incapacitating emotional outbursts. In conversations she was quickly exhausted and discouraged.

She was given a simple group of tests to perform. First, she had to name five objects (fork, soap, pencil, rubber eraser, light bulb). Second, she had to indicate by word or action what these objects were used for. Third, she was given the Goldstein-Scheerer block test. The performance in each situation was recorded in detail. Then a 5 per cent solution of sodium amytal was injected slowly intravenously. After she had received about 4 cc., the patient displayed a sudden change in mood, which indicated that the optimum end point of the injection had

From the Neurological Service of the Mount Sinai Hospital.

1. Linn, L., and Stein, M.: The Use of Sodium Amytal in the Treatment of Aphasia, Bull. U. S. Army M. Dept. 5:705 (June) 1946.

been reached. Instead of her usual irritable, discouraged, querulous manner, she became cheerful and relaxed. She spoke spontaneously and easily. The foregoing tests were repeated. Her performance was strikingly improved. She succeeded in completing in a few seconds tasks which previously took minutes of painful, futile struggle. A striking feature of the performance following the injection was her ability to sustain over a long period of time her attention and energy output. She left the hospital shortly after this one observation, and it was not possible to carry out further tests with her.

CASE 2.—R. W., a woman aged 47, on Nov. 23, 1945 had sudden onset of right hemiplegia with aphasia. A diagnosis of cerebral thrombosis was made, and she was admitted to Mount Sinai Hospital. The hemiplegia cleared up in a short time, but the aphasia persisted. The patient was practically mute. She was given an intravenous injection of sodium amytal in the manner described in the first case. A striking improvement in her speech resulted. However, as the effect of the drug wore off she lapsed into her previous state of mutism. With repeated injections, the ability of the drug to produce this transitory improvement was gradually lost. At this time the patient is, once again, practically mute.

COMMENT

This material is presented as a brief note for the purpose of bringing promptly to the attention of a wider circle of physicians this interesting and useful procedure. It has long been known that many cases of impairment in cerebral function have an emotional overlay. The aphasic person who cannot speak the words of a verse can sometimes sing them, and in response to sufficient emotional pressure may be able to utter expletives which he cannot speak as single words. The patient with *paralysis agitans* who is rigid and bent has been known to become capable of performing acts requiring considerable agility under certain conditions.

Obviously, sodium amytal does not reverse an organic process. However, its use in the manner described not only may make it possible to hasten the rehabilitation of patients with post-traumatic aphasia, but may afford opportunities to explore the psychologic component in many apparently hopeless cases of organic disease of the brain.

70 East Eighty-Third Street (28).

Case Reports

SUBARACHNOID CERVICAL ANGIOMA WITH CUTANEOUS HEMANGIOMA OF A CORRESPONDING METAMERE

Report of a Case and Review of the Literature

CAPTAIN GLEN O. CROSS, MEDICAL CORPS, ARMY OF THE UNITED STATES

THE WIDER recognition of the relationship between developmental anomalies of the skin and coexisting abnormalities of other ectodermal derivatives, particularly the nervous system, is important clinically. Early surgical relief when such lesions are compressing the adjacent structures of the central nervous system is imperative, and too long a delay causes irreparable damage. This has been repeatedly emphasized by a number of authors. As early as 1895 Berenbruch¹ noted the relation of cutaneous angiomas, lipomas and vascular tumors of the spinal cord. He was able to demonstrate actual vascular connections between an angioma of the cervicothoracic portion of the spinal cord and multiple angioliomas of the skin of the upper part of the trunk in a case reported at that time, the connecting vessels in that instance passing by way of the intervertebral foramen. Cushing and Bailey,² in their monograph on vascular tumors, pointed out that the skin and other organs lying in the same segment of nerve distribution are often affected when a vascular abnormality of the central nervous system exists. He reported nevi of the face associated with intracranial vascular tumors. There have been numerous subsequent reports of similar lesions; however, according to Turner and Kernohan,³ instances of vascular tumors of the cord associated with nevi of the corresponding cutaneous segments were reported only four times prior to 1941. The first report of that nature was one by Cobb⁴ in 1915. He collected 7 cases of subdural angioma from the literature, 1 of which was Berenbruch's previously mentioned case. The latter was the only case with associated cutaneous nevi. Rand,⁵ in 1927, described a case of hem-

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1. Berenbruch, K.: Ein Fall von multiplen angioliomen kombiniert mit einem Angiom des Rückenmarks, Deutsche Ztschr. f. Nervenhe. **6**:127-136, 1895.

2. Cushing, H. W., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C Thomas, Publisher, 1928.

3. Turner, O. A., and Kernohan, J. W.: Vascular Malformations and Vascular Tumors Involving the Spinal Cord, Arch. Neurol. & Psychiat. **46**:444-463 (Sept.) 1941.

4. Cobb, S.: Haemangioma of the Spinal Cord Associated with Skin Naevi of the Same Metamere, Ann. Surg. **62**:641-649, 1915.

5. Rand, C. W.: Hemangioma of the Spinal Cord, Arch. Neurol. & Psychiat. **18**:755-765 (Nov.) 1927.

angioma with an associated nevus of the back. In Johnston's⁶ case, reported in 1938, an epidural hemangioma of the spinal cord was associated with a cutaneous nevus over the tenth rib posteriorly. The next case was reported by Karshner, Rand and Reeves⁷ in 1939. If Berenbruch's case is included as the first one to be reported, a total of 5 cases was reported prior to the present case. The distribution of the "external sign posts" (Cushing and Bailey²) in the aforementioned cases is shown in figure 1. It will be seen that the present case is the only one with a cutaneous lesion of the cervical region. This is interesting in view of the report of Ward and Covington,⁸ that the nape of the neck is the most frequent location for superficial hemangiomas of the skin. This observation is supported by the studies of Watson and McCarthy⁹ on a series of 1,056 cases of hemangioma of the skin. They reported that 50 per cent of these lesions occurred in the region of the neck, although this area makes up less than one seventh of the total body surface. Rasmussen, Kernohan and Adson,¹⁰ reporting on a series of 557 tumors of the cord, found 52 to be tumors of blood vessels, with 19 per cent located in the cervical, 64 per cent in the thoracic and 17 per cent in the lumbar region. This would help to explain the rarity of the association of hemangiomas of the skin of the neck with vascular abnormalities of the cervical portion of the cord, as the abnormalities of the cord are comparatively rare in that locale. Turner and Kernohan,³ in their study of 46 cases of vascular tumors of the spinal cord, which included 18 cases of angioma, stated that in no case was there any cutaneous vascular or pigmented nevus. Cobb,⁴ in his report, referred to a case of a large angioma of the right flank, associated with clinical signs of tumor of the cord, which terminated fatally; but as no operation or postmortem examination was made he did not include this case in his series. Elsberg¹¹ referred to a case reported by Alexander in 1922. No reference was found in the literature of that time to this publication. Reported instances of hemangioma of the vertebral bodies associated with angiomas of the skin were found.

6. Johnston, L. M.: Epidural Hemangioma with Compression of the Spinal Cord, *J. A. M. A.* **110**:119-122 (Jan. 8) 1938.
7. Karshner, R. G.; Rand, C. W., and Reeves, D. L.: Epidural Hemangioma Associated with Hemangioma of the Vertebrae, *Arch. Surg.* **39**:942-951 (Dec.) 1939.
8. Ward, G. E., and Covington, E. E.: Hemangiomas of the Skin, *J. A. M. A.* **114**:2069-2075 (May 25) 1940.
9. Watson, W. L., and McCarthy, W. D.: Blood and Lymph Vessel Tumors, *Surg., Gynec. & Obst.* **71**:569-588 (Nov.) 1940.
10. Rasmussen, T. B.; Kernohan, J. W., and Adson, A. W.: Pathological Classification with Surgical Consideration of Intraspinal Tumors, *Ann. Surg.* **111**:513-530 (April) 1940.
11. Elsberg, C. A.: *Tumors of the Spinal Cord*, New York, Paul B. Hoeber, Inc., 1925, pp. 203-205.

Ferber and Lampe¹² recorded a case in which there were many small hemangiomas of the skin of the back and abdomen in the region of the fifth to the tenth thoracic spinal segments, with corresponding neurologic signs. There was roentgenographic evidence of hemangioma of the seventh thoracic vertebra with obstruction of the spinal canal and compression of the cord. The patient was successfully treated with roentgen radiation. Topfer¹³ studied 2,154 cadavers, in 256 of which (about 12 per cent) he observed hemangiomas of the vertebrae associated with lipomas of the skin in corresponding metameres. Elsberg¹⁴ stated that he operated in a case in which a large mass of fat filled with dilated veins was observed in the subcutaneous fat of the

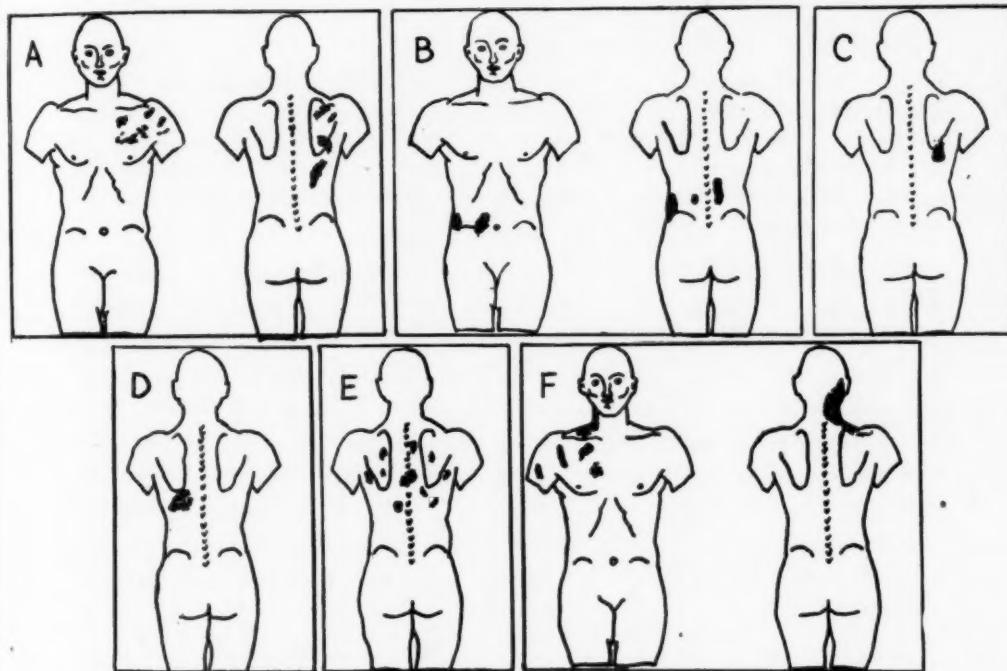


Fig. 1.—Distribution of the cutaneous angiomas in the cases reported in the literature. *A*, Berenbruch's case (1895); *B*, Cobb's case (1915); *C*, Rand's case (1927); *D*, Johnston's case (1938); *E*, Karshner, Rand and Reeve's case (1939); *F*, present case.

back overlying a spinal varicosity of the fourth thoracic segment. Blackford,¹⁵ in 1943, reported a case of hemangioma of the eleventh thoracic

12. Ferber, L., and Lampe, I.: Hemangioma of the Vertebrae Associated with Compression of the Cord, *Arch. Neurol. & Psychiat.* **47**:19-29 (Jan.) 1942.

13. Topfer, cited by Karshner, Rand and Reeves.⁷

14. Elsberg, C. A.: *Diagnosis and Treatment of Surgical Diseases of the Spinal Cord and Its Membranes*, Philadelphia, W. B. Saunders Company, 1916.

15. Blackford, L. M.: Hemangioma of the Vertebrae with Compression of the Cord, *J. A. M. A.* **123**:144-146 (Sept. 18) 1943.

vertebra associated with a tumor 4 cm. in diameter, protruding 2 to 3 cm. over the right half of the vertebra. This tumor was said to "look and feel like a mass of tangled veins." Ehni and Love¹⁶ reviewed the literature up to 1945 and reported 29 cases of intradural lipoma. Five of their series of extradural tumors were classified as "angiolipoma"; 1 was called "angioma with fat cells," and 1 a "vascular lipoma." In 5 of the total series lipomas occurred in corresponding segments of the skin. In their discussion of these cases they mentioned the possibility that lipoma and angioma are related neoplasms and stated:

... This brings to mind the case reported by Cobb [4] . . . These cases seem to indicate the participation of common mesenchyme with an abnormal potentiality for the formation of tumor in the genesis of the pia.

They summarized their study by saying:

... Neurofibromatosis has been related to Lindau's disease and to Sturge-Weber disease, and the group of diseases has been termed congenital ectodermosis. . . . There appear to be reasons for including multiple lipomatosis in the group [of phacomatoses]. . . . There is a close relation between angioma and lipoma. Intraspinal lipoma appears to be related to neurofibromatosis and the other "phacomatoses."

Cushing and Bailey² called attention to Lindau's belief that the hemangioma of the cerebellum was part of a more generalized systemic disorder, which he called "angiomatosis of the central nervous system," and that it was often accompanied with cystic formations in the pancreas, kidneys, liver and testes and, more rarely, with hypernephroma.

It would seem to be accepted that vascular tumors of the spinal cord are but part of a widespread process. In the cases discussed here the tumor of the spinal cord was discovered because it presented symptoms and was associated with vascular abnormalities of the skin, while other developmental anomalies which may have been present were asymptomatic.

REPORT OF CASE

History.—On Oct. 3, 1944, a Mexican aged 19, a soldier, was admitted to a station hospital overseas with complaints of weakness of the left arm and leg and pain in the right leg. His past history revealed that he had previously been hospitalized in December 1943 because of persistent sharp pains in the right ankle. There was noticeable weakness of the left arm at that time. As no apparent cause for his symptoms was then found, he was discharged to return to duty. In May 1944, after a period of progressive ascent of the pain in the right leg, there developed severe pain in the right hip and iliac region. Because appendicitis was suspected, he was hospitalized; but the diagnosis was not confirmed, and he was again returned to duty. For two months prior to his last admission to the hospital he had noticed progressive difficulty on arising in the morning because of pain in the right leg and stiffness of the left leg and arm. He stated that the left leg

16. Ehni, G., and Love, J. G.: Intradural Lipomas, Arch. Neurol. & Psychiat. 53:1-28 (Jan.) 1945.

and hand seemed to be "wasting away." Examination on October 3 revealed beginning clawhand on the left. There were almost complete loss of grip in this hand, and atrophy of the musculature of the left arm was estimated at 50 per cent. No sensory abnormalities were elicited. The left leg showed loss of muscular power and "20 per cent atrophy." The deep reflexes were hyperactive, but no pathologic toe signs were observed. There was an exhaustible ankle clonus on the left. Laboratory studies at that hospital revealed no abnormalities. He was sent to a general hospital on October 11 with a diagnosis of "hemiplegia, left, incomplete, cause undetermined." Examination at that hospital revealed, in addition, bilaterally hyperactive knee jerks and a positive Babinski sign on the left, and



Fig. 2.—Myelogram showing almost complete block at the interspace between the fifth and sixth cervical vertebrae.

lowered cutaneous temperature over the left upper and lower extremities. Fibrillations were observed in the musculature of the left thigh. Paresthesias to pinprick were noted over the left lower extremity. A laboratory survey, including roentgenograms of the complete vertebral column, studies of the spinal fluid and its dynamics and gastric analysis, revealed no pathologic condition. He was returned to the United States with the tentative diagnosis of "amyotrophic lateral sclerosis" and was admitted to the DeWitt General Hospital on April 14, 1945.

Examination.—In addition to the signs already recorded, the patient presented a hemangioma of the skin of the left side of the neck and prominent vascular

markings of the skin of the upper part of the chest and over the seventh cervical and first thoracic vertebral spines. The biceps and triceps reflexes were more active on the left side than on the right. The abdominal and cremasteric reflexes were absent on the left side. There were a positive Hoffmann sign and a classic left Babinski sign on the left side. There was pversion of sensation over the left side of the body, described as "a feeling like an electrical shock," when the skin was stroked with a pinpoint. Position sense was lost in the left great toe. Vibratory sense was normal. The body temperature was higher on the right side than on the left. There were mild hypesthesia of the right side of the face and hypo-



Fig. 3.—Exposure of the hemangioma in the cervical region.

thesia of the left side of the palate, and the uvula drew up to the right. There was a congenital coloboma of the left iris. No hemangiomas were seen in the retina, and the disks were normal.

Laboratory Studies.—The blood count revealed 5,000,000 red cells; 90 per cent (15 Gm. per hundred cubic centimeters) hemoglobin, and 7,000 white cells, with a differential count of 1 basophil, 3 eosinophils, 49 segmental forms, 44 lymphocytes and 3 mononuclear cells. The hematocrit reading was 44. The sedimentation rate was 1 mm. in one hour. The Kahn reaction of the blood was negative. The urine was cloudy and yellow, with a specific gravity of 1.021 and an acid reaction.

Spinal puncture and manometric study of the spinal fluid, done after the method of Grant and Cone, indicated a subarachnoid block. The total protein of the spinal fluid was 28.5 mg. per hundred cubic centimeters.

In view of the neurologic findings and the manometric readings, with the presence of the hemangioma of the skin, the possibility of a hemangioma of the upper cervical portion of the cord was considered. A myelogram, taken with 6 cc. of "pantopaque" (a mixture of ethyl esters of isometric iodophenylundecylic acid), showed almost complete block of the canal at the interspace between the fifth and sixth cervical vertebrae (fig. 2).

Operation (Dr. Frank Echlin).—With the use of endotracheal anesthesia, a laminectomy was done on the fifth, sixth and seventh cervical vertebrae. The dura was opened, and an extensive mass of subarachnoid blood vessels was seen. These vessels extended upward to the upper limits of the dural opening. The laminectomy was extended to the second cervical vertebrae, and the dura was opened as far as the atlas. The varix was seen to extend beneath the lamina of the axis into the posterior fossa. The vessels were of mixed arterial and venous type. The vascular mass was so dense that the cord could not be seen except below the sixth cervical segment. The cord at that level appeared compressed and flattened. The large blood vessels measured up to 4 cm. in diameter and were continuous with the vessels in the spinal cord.

Because the upper extent of the vessels could not be determined and because of the continuity of the vessels with those of the cord, no attempt was made to remove the varix, in view of the danger of development of transverse myelitis. The question of placing a fascial transplant in the dura to decompress the varix was considered, but the dura could be closed over the varix, leaving approximately $\frac{1}{2}$ inch (1.3 cm.) of space between the vessels and the dura posteriorly. The dura was accordingly closed, and the other tissues were closed in layers over the wound.

Postoperative Course.—Recovery was uneventful. The patient was relieved of the pain in the right arm and leg. He was furnished with a brace for the neck and was ambulatory in three weeks. He was then given high voltage roentgen therapy to the posterior portion of the neck, receiving 1,400 r over a period of eight days. This did not alter his clinical picture to any appreciable degree, possibly because of the large size of the vessels. A reinfection type of pulmonary tuberculosis then developed, and the patient was transferred to a veterans administration facility.

COMMENT

The progress of the symptoms in this case followed the course presented by Oppenheim and Frazier¹⁷ for extramedullary tumors of the spinal cord. They divided the signs and symptoms into three phases: (1) involvement of the nerve roots (pain); (2) beginning compression of the spinal cord (motor weakness), and (3) extreme compression of the spinal cord (paralysis and transverse myelitis). Globus and Doshay,¹⁸ in their discussion of 42 cases of vascular tumors of the cord, describe pain as the most frequent early sign. It was

17. Oppenheim and Frazier, cited by Rasmussen, Kernohan and Adson.¹⁹

18. Globus, J. L., and Doshay, L. J.: Venous Dilatations and Other Intra-spinal Vessel Alterations Including True Angiomata with Signs and Symptoms of Cord Compression, *Surg., Gynec. & Obst.* **48**:315-366 (March) 1929.

present in 46 per cent of their cases as the first symptom. Motor weakness was present in 12 of their cases, while paresthesia was a feature in only 3 cases. In contrast to the myelographic findings in the present case, Globus and Doshay¹⁸ stated that in their series studies made in a few cases with iodized poppyseed oil revealed no block. Delmas-Marsalet,¹⁹ however, described a "characteristic appearance" of hemangiomas of the cord in the myelogram. Elsberg¹¹ pointed out that the signs and symptoms of spinal varices are sometimes indistinguishable from those produced by tumors of the cord and cautioned against always accepting the varices as the sole lesions without looking for a tumor or other lesion at a higher level which may be causing venous obstruction and dilatation.

SUMMARY

A case of hemangioma of the cervical portion of the spinal cord associated with cutaneous hemangiomas of the corresponding metameres is presented.

The 5 previously reported cases are reviewed.

The apparent close relationship of the various abnormalities of development of the ectodermal derivatives and the importance of their clinical recognition are stressed.

19. Delmas-Marsalet, P.: Poussées évolutives gravidiques et image lipiodolée caractéristique des hémangiomes médullaires, *Presse méd.* **49**:964-965 (Sept. 10-13) 1941.



News and Comment

RESIDENCY TRAINING PROGRAMS OF VETERANS ADMINISTRATION

Two new residency training programs for physicians desiring to train in neurology under the Veterans Administration have been organized. The residencies are designed to prepare residents for certification in neurology by the American Board of Psychiatry and Neurology.

The first new program will be conducted under the auspices of the New York University and the neurologic service of the Psychiatric Division of the Bellevue Hospital, New York. The program provides for training at Bellevue Hospital and the Veterans Administration New York Regional Office. The staff includes Dr. S. Bernard Wortis, Dr. E. D. Friedman, Dr. Lewis Stevenson, Dr. Samuel Brock, Dr. M. B. Bender and Dr. Margaret Kennard. Applications should be sent to Dr. S. Bernard Wortis, chairman, Deans Subcommittee for Neurology, New York University, 400 East Thirtieth Street, New York.

The second new program has been organized by the George Washington School of Medicine and the Georgetown University School of Medicine. Residents will be offered training facilities at the Veterans Administration Hospital (Mount Alto), Washington, D. C.; Gallinger Municipal Hospital, the Veterans Administration Regional Office, Children's Hospital and the Army Institute of Pathology. The staff includes Dr. Walter Freeman, Dr. Norman Q. Brill, Dr. James Watts, Dr. Webb Haymaker, Dr. Paul Chodoff, Dr. Harold Stevens and Dr. Othmar Solnitzy. Applications should be forwarded to Dr. Walter Freeman, chairman, Deans Subcommittee for Neurology, 2014 R Street, Northwest, Washington, D. C.

Other medical schools affiliated with the Veterans Administration for residency training in neurology where training programs are already under way, are:

Medical School	Location of Veterans Administration Hospitals and Clinics	Applications Received by
Cornell University Medical College... Columbia University College of Physicians and Surgeons	Bronx, N. Y.	Dean Willard C. Rappleye, 630 West One Hundred Sixty-Eighth Street, New York
Northwestern University Medical School University of Illinois College of Medicine	Hines, Ill.	Dr. Lewis J. Pollock, Northwestern University Medical School, Chicago
University of Minnesota Medical School	Minneapolis	Dean Harold S. Diehl, University of Minnesota Medical School, Minneapolis 14
Boston University School of Medicine Tufts College Medical School Harvard Medical School	Framingham, Mass.	Dr. Harry C. Solomon, Chairman, Deans Subcommittee for Neuropsychiatry, Harvard Medical School, Boston
Jefferson Medical College of Philadelphia	Coatesville, Pa.	Dr. Edward A. Strecker, Chairman, Deans Subcommittee for Neuropsychiatry, 111 North Forty-Ninth Street, Philadelphia 39

ADOLF MEYER GIFT TO SETON INSTITUTE

The Medical Advisory Board of the Seton Institute and the Sisters of Charity of St. Vincent de Paul are pleased to announce the gift from Dr. Adolf Meyer of his entire personal collection of neuroanatomic and neuropathologic material, consisting of some sixty large boxes of serial sections from crucial human case

material, as well as material of a comparative nature. Included in the gift is an exhaustive card index file of neurologic subjects.

The Seton Institute plans to use this material as the nucleus about which to develop a laboratory for the study of neuroanatomy, neurophysiology and neuropathology.

The material will soon be in available form for the instruction of candidates for the American Board examinations in neurology.

The institute is deeply indebted to Dr. Meyer for this magnificent gift, and in recognition of his generosity the laboratory will be named the Adolf Meyer Laboratory of Neurology.

SOUTHERN PSYCHIATRIC ASSOCIATION

The officers and fellows of the Southern Psychiatric Association announce that their annual meeting will be held in Birmingham, Ala., on Oct. 13 and 14, 1947.

AMERICAN BOARD OF NEUROLOGICAL SURGERY

On June 3, 1947 Dr. William J. German, 310 Cedar Street, New Haven, Conn., was elected secretary-treasurer of the Board, to replace Dr. Paul C. Bucy, Chicago, whose term of office has expired.

WARTIME TRAINING CREDIT ALLOWED BY THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

In order to avoid misunderstanding regarding the allowance of one year of training credit for work in the armed forces during wartime, it should be noted that wartime to this Board means V-J Day plus six months.

Therefore, men who entered the service on V-J Day would be allowed six months' credit. Men who entered the armed forces after February 1946 will not be granted credit toward the training requirements unless they were residents in hospitals approved by this Board for residency training. If they have practiced psychiatry or neurology during this time, however, it is probable that this will be counted toward the requirements for experience.

F. J. BRACELAND, Secretary-Treasurer.

THE WOODS SCHOOLS TO BECOME A NONPROFITABLE, CHARITABLE CORPORATION

Mrs. Mollie Woods Hare, founder and active head of the Woods Schools, Langhorne, Pa., applied on June 9, 1947, to the Bucks County Court, at Doylestown, Pa., to make an outright gift of the \$2,500,000 school property to a nonprofitable, charitable corporation. The corporation, to be known as The Woods Schools, is to be administered by a self-perpetuating board of trustees from five to fifteen members.

The school was founded thirty-one years ago for the express purpose of teaching the exceptional child—the child who, for whatever reason, does not fit into the usual educational program. Throughout its entire existence the school has concentrated on this field of education, with consistently successful results. It has always maintained extremely small classes so as to give personal attention to each student. For the last thirteen years it has conducted the internationally known Child Research Clinic with an advisory board of outstanding medical and educational authorities. The clinic was founded in 1934, at the urgent requests

of psychologists and educators that the findings of the Woods Schools relative to dealing with the exceptional child be made available both to the public and to scientific circles.

Mrs. Mollie Woods Hare began her teaching career in the public schools of Philadelphia. It was during this period that she became increasingly impressed with the problem of individual differences in children. She gained her educational experience and insight in her own classroom, as well as in her studies. She became convinced finally that only a school especially planned to train the many types of exceptional children could salvage the latent possibilities of the handicapped child. From this conviction was born the Woods Schools, which, under Mrs. Hare's direction, has expanded to its present national recognition. In 1939 Mrs. Hare was awarded the honorary degree of Doctor of Humane Letters by Temple University, Philadelphia, for her outstanding accomplishments in the field of education.

Abstracts from Current Literature

Physiology and Biochemistry

EFFECT OF CONCUSSION UPON THE POLARIZABILITY OF THE BRAIN. E. A. SPIEGEL, G. C. HENNY, H. T. WYCIS and M. SPIEGEL-ADOLF, Am. J. Physiol. 146:12 (April) 1946.

The polarizability of the cerebrum was studied in cats and guinea pigs after concussive and subconcussive blows produced by a pendulum. Subconcussive blows did not materially alter the polarizability, but severe concussive blows produced a significant decrease. This alteration is a reversible process and indicates an injury to cell membranes. The decrease in polarization is a secondary change, reaching its maximum after the fleeting functional disturbances characteristic of concussion have subsided.

FORSTER, Philadelphia.

EFFECTS OF LOCAL APPLICATIONS OF ACETYLCHOLINE TO THE ACOUSTIC CORTEX. FRANCIS M. FORSTER and ROBERT H. McCARTER, J. Neuropath. & Exper. Neurol. 5:24 (Jan.) 1946.

The study was initiated to determine the effects of applications of acetylcholine to the auditory receptive area. Fifteen adult cats were studied. Anesthesia was induced with "dial with urethane" in doses of 0.45 to 0.5 cc. per kilogram of body weight. (Each cubic centimeter contains 0.1 Gm. "dial" [diethylmalonylurea], 0.4 Gm. urethane, 0.4 Gm. monoethylurea and water q. s.) The hemispheres were exposed; the dura was reflected, and silver chloride electrodes were used. Recording was by means of a three channel, condenser-coupled ink-writing oscillograph (Grass). Auditory stimuli were administered by clicking a contact key, which was wired in circuit with a signal magnet so arranged as to deflect one writer of the oscillograph. Acetylcholine was applied in concentrations of 5 to 10 per cent and on filter paper pledges 1 to 2 mm. square. The pledges were blotted to remove excess acetylcholine.

It was found that the application of acetylcholine to the exposed acoustic cortex of the cat produced a depression of the spontaneous electrical activity of the cortex and of the sound-induced electrical spikes. This was followed by enhancement of the sound-induced spikes, by the appearance of spontaneous acetylcholine-induced discharges and by an after-discharge similar to the spontaneous acetylcholine discharges. Shortly after the appearance of the acetylcholine discharges it was possible to prevent the appearance of these discharges by appropriately timed sound stimuli, so that the cortex was driven in a pattern of augmented auditory spikes and free from acetylcholine discharges. After the acetylcholine discharges had been present for several minutes, usually two to three, it was no longer possible to eliminate the acetylcholine discharges with this procedure.

Distant response to auditory stimulation was also obtained. Spiking discharges in response to auditory stimuli were obtained from a region of the medial suprasylvian gyrus only after the application of acetylcholine to this area resulted in spontaneous acetylcholine discharges. These spiking discharges were synchronous with those obtained in the previously determined acoustic cortex of the upper sylvian gyrus. The spiking discharges of the distant area in response to auditory

stimuli could not be elicited prior to the application of acetylcholine or after the effects of application had disappeared.

Forster and McCarter state that there is a probable correlation between the cortex treated with acetylcholine and the epileptic cortex, and this makes it extremely likely that an area of cortex presenting the pattern of intermittent acetylcholine discharges is undergoing a seizure disturbance.

GUTTMAN, Philadelphia.

REFLEX PUPILLODILATOR MECHANISMS: AN EXPERIMENTAL ANALYSIS. ALBERT KUNTZ and CALVIN A. RICHINS, *J. Neurophysiol.* 9:1 (Jan.) 1946.

Kuntz and Richins studied the reflex pupillodilator mechanisms in cats and dogs. Parasympathetic denervation of the eye was found to produce pronounced enlargement of the pupil, but not to the point of maximum dilatation. Maximal dilation probably requires active contraction of the radial muscle of the iris, which is innervated by sympathetic nerves.

Painful stimuli administered peripherally elicited moderate reflex dilation of the pupil. Sympathetic denervation of the eye did not alter this response, but section of the oculomotor nerve or extirpation of the ciliary ganglion abolished the dilatation. Pupillary dilation due to peripheral painful stimulation is therefore mediated through the parasympathetic nerves. After transection of the lower cervical region of the cord strong stimulation of the hindfoot or of the exposed sciatic nerve produced slight enlargement in animals under pentobarbital anesthesia but no response in nonanesthetized animals. The authors conclude that this observation indicates increased excitability of the ciliospinal center due to the anesthetic agent.

When the pupils have been dilated with atropine, moderate stimulation of the oculomotor nerve produces further dilation. Pupillary dilation following peripheral stimulation is greatly decreased after the intravenous administration of ergotoxine. Kuntz and Richins conclude that these results support the assumption that the pupillodilator reaction mediated through the parasympathetic center of the mesencephalon is actively integrated and controlled and that activation of this center produces inhibition of the circular muscle of the iris. FORSTER, Philadelphia.

EFFECTS OF INHIBITORS OF CHOLINE ESTERASE ON THE NERVE ACTION POTENTIAL. THEODORE H. BULLOCK, DAVID NACHMANSON and MORTIMER A. ROTHENBERG, *J. Neurophysiol.* 9:9 (Jan.) 1946.

Bullock, Nachmansohn and Rothenberg studied the effect of inhibitors of cholinesterase on the action potential of the giant axon and the fin nerve of the squid. Physostigmine alters, and in high concentration abolishes, the action potential of both the giant axon and the fin nerve. The authors point out that this effect is consistent with the concept that acetylcholine is the depolarizing agent released during the passage of the impulse and that the physiologic role of cholinesterase should be the rapid removal of the ester, and that therefore the inhibition of cholinesterase should result in enduring depolarization and abolition of conductivity. The effect of physostigmine is easily reversible. Neostigmine was found to have no effect on the action potential. The difference in the effect of physostigmine and that of neostigmine is explained by the fact that neostigmine is a quaternary ammonium compound and cannot penetrate a lipid membrane, while physostigmine is a tertiary amine and can pass through a lipid membrane. Acetylcholine is also a quaternary ammonium compound and therefore does not alter conductivity when applied externally to the axon but is effective when applied at nerve endings. Bullock, Nachmansohn and Rothenberg conclude that their observations are consistent with the concept that the physicochemical mechanism of conduction along the axon does not differ fundamentally from that in transmission across synapses.

FORSTER, Philadelphia.

THE EFFECT OF CELLULAR HYDRATION ON EXPERIMENTAL ELECTRO-SHOCK CONVULSIONS. EWART A. SWINYARD, JAMES E. P. TOMAN and LOUIS S. GOODMAN, *J. Neurophysiol.* 9:47 (Jan.) 1946.

Swinyard, Toman and Goodman produced cellular hydration in rats by depletion of 40 per cent of extracellular electrolyte without change in the total water content of the body. Under these conditions the threshold of electric shock seizure was lowered by an average of 56 per cent. Cellular hydration of the same degree produced by oral administration of water altered the seizure threshold to an equal degree. When these two methods of cellular hydration were combined, a synergistic effect was observed, and seizures occurred spontaneously. The threshold for metrazol convulsions followed the same alterations as did the threshold for electric shock convulsions. Rapid replacement of electrolytes increased the threshold of electric shock convolution, and electrolyte given to normal rats raised the normal seizure threshold. An increase in volume of extracellular fluid without alteration of cell volume or concentration of electrolyte does not lower the seizure threshold. The authors conclude that cellular hydration decreases and cellular dehydration increases the seizure level independently of changes in volume of extracellular fluid. Not all antiepileptic drugs raise the normal convulsive threshold. But diphenylhydantoin, phenobarbital and trimethadione ("tridione") significantly raise the threshold of electric shock convolution lowered by cellular hydration.

FORSTER, Philadelphia.

SYNAPTIC POTENTIALS OF MOTONEURONES. J. C. ECCLES, *J. Neurophysiol.* 9:87 (March) 1946.

Eccles subjected the motoneurons of the cat and frog spinal cords to direct synaptic excitation by a single, synchronous volley of impulses and recorded from the ventral root fibers the resulting potential changes. Blocking of synaptic transmission by deep anesthesia did not interfere with the synaptic potential, a negative change in the motoneuron which was propagated electrotonically along the ventral root fibers. The durations of latent period, rising phase and exponential decay were determined. Synaptic potentials due to two volleys or to repetitive stimuli were summated. Eccles could find no evidence of enduring depolarization, such as occurs in sympathetic ganglia with high frequency stimulation. In unanesthetized animals synaptic potential preceded motoneuron impulses by 0.2 to 0.3 millisecond. Barely blocking the synaptic potential by deepening anesthesia allows the demonstration of facilitation of the response by a second volley administered within fifteen milliseconds. This facilitation is apparently the result of summation of synaptic potentials. The factors governing synaptic transmission would appear to be the synaptic potential acting as a catelectrotonus and the stability of the motoneuron's surface membrane. Blocking of transmission with pentobarbital anesthesia does not affect the time course of the synaptic potential but is effective largely by stabilizing the motoneuron cell membrane and, to a less extent, by diminishing the production of synaptic potential. Synaptic transmission action is of short duration. Curarine was found to have a strychnine-like action on the spinal cord. Physostigmine had no effect on synaptic potentials, and Eccles concludes that acetylcholine plays no important role in synaptic transmission in the spinal cord.

FORSTER, Philadelphia.

THE PYRAMIDAL TRACT: EFFECT OF MAXIMAL INJURY ON ACID PHOSPHATASE CONTENT IN NEURONS OF CATS. WALTER L. HARD and A. M. LASSEK, *J. Neurophysiol.* 9:121 (March) 1946.

Hard and Lassek performed massive cortical removal of the left hemisphere of cats and studied after various survival times the presence or absence of acid phosphatase in both pyramidal tracts. The enzyme was found to disappear from

the axons of the pyramidal tract between the second and third day after cortical removal. The earliest changes were observed in the larger axis-cylinders. During the course of secondary degeneration the enzyme does not reappear. Hard and Lassek conclude that the acid phosphatase technic is a delicate method for determining the integrity and course of degeneration of axis-cylinders following maximal injury to the cells of origin. The presence of the enzyme for a time after destruction of the cells of origin would indicate that the functional activity persists despite the separation of the tissue from the cells of origin. Moreover, in view of the role of phosphatase in phospholipid metabolism, the possibility arises that the axon through its enzyme systems plays an important role in maintaining the integrity of the myelin sheath.

FORSTER, Philadelphia.

A CORTICO-BULBO-RETICULAR PATHWAY FROM AREA 4s. W. S. McCULLOCH, C. GRAF and H. W. MAGOUN, *J. Neurophysiol.* 9:127 (March) 1946.

McCulloch, Graf and Magoun demonstrated by means of the strychnine technic in monkeys a descending connection from the cortical area 4s. This descending pathway diverges from the pyramidal tract in the medulla and apparently ends in the bulbar reticular formation. Since applications of strychnine do not produce strychnine spikes beyond a synapse, the pathway is presumably a direct one. It is not certain whether or not this pathway is myelinated below the pons. Stimulation of area 4s produces relaxation; destruction of this area produces spasticity. The pathway described by McCulloch, Graf and Magoun terminates in a bulbar region, stimulation of which produces relaxation. The authors conclude that the cortico-bulboreticular pathway from area 4s is an extrapyramidal system mediating relaxation.

FORSTER, Philadelphia.

PYRUVIC ACID EXCHANGE OF THE BRAIN. WILLIAMINA HIMWICH and HAROLD E. HIMWICH, *J. Neurophysiol.* 9:133 (March) 1946.

Himwich and Himwich studied the pyruvic acid content of the blood from the internal jugular vein and from an artery in quietly resting, postabsorptive patients. The cerebral venous blood was found to contain small, but significant, increments of pyruvic acid, averaging 0.22 mg. per hundred cubic centimeters. Himwich and Himwich conclude that the brain constantly produces energy without the equivalent utilization of oxygen and that the carbohydrate metabolism of the brain includes not only that portion which is oxidized but also the part split into lactic and pyruvic acids.

FORSTER, Philadelphia.

AN INHIBITORY MECHANISM IN THE BULBAR RETICULAR FORMATION. H. W. MAGOUN and R. RHINES, *J. Neurophysiol.* 9:165 (May) 1946.

Magoun and Rhines observed in cats the blink, flexor and patellar reflexes and the motor responses to stimulation of the motor cortex and the internal capsule. The effects on these movements of bipolar stimulation of the lower portion of the brain stem were observed. The authors found that the bulbar segment of the brain stem contains neural elements capable of exerting an inhibitory influence on a wide variety of motor performances. Motor activity initiated reflexly, by decerebration or by stimulation of the motor cortex, was inhibited. Histologic study of the brain stems revealed that the inhibitory region was distributed in the bulbar reticular formation, especially in the ventromedial portion, and that from this region efferent connections descended to the ventral part of the cord.

FORSTER, Philadelphia.

Neuropathology

MYELOMALACIA OF THE CERVICAL PORTION OF THE SPINAL CORD, PROBABLY THE RESULT OF ROENTGEN THERAPY. LEWIS D. STEVENSON and ROBERT E. ECKHARDT, *Arch. Path.* **39**:109 (Feb.) 1945.

A man received intensive radiation therapy to the cervical region for lymphoepithelioma of the nasopharynx. About two years later signs of transverse myelitis developed in the region of the fourth cervical segment. The myelitis progressed and eventually led to death from respiratory paralysis. At laminectomy the cord appeared normal. Further radiation therapy was without effect on the course of the disease. Postmortem examination revealed myelomalacia of the cervical part of the cord, in the vicinity of which many thickened arterioles with fibrous walls could be seen. This reaction is believed to be an unusual one to roentgen radiation therapy directed to the neck, but one which must be kept in mind when such therapy is contemplated.

WINKELMAN, Philadelphia.

THE BRAIN IN LEUKEMIA. FRANZ LEIDLER and WILLIAM O. RUSSELL, *Arch. Path.* **40**:14 (July) 1945.

A clinical and pathologic study of 20 brains selected at random from persons who died of leukemia was made to determine the type and extent of the pathologic changes occurring in the brain in this disease and to correlate them with the clinical neurologic signs. The gross pathologic study of the brain was carried on as the organ was serially sectioned by means of a slicing machine, the individual slices being not more than from 3 to 5 mm. thick.

In a review of the literature, the authors collected 47 cases of leukemia in which adequate pathologic study of the brain was made; to this group they added the 20 cases on which the aforementioned study was based.

Hemorrhage and infiltration of leukemic cells in the brain, occurring separately or together, were the only significant pathologic changes that could be directly attributed to the leukemic disease. One or both of these pathologic changes were present in 62 of the cases. They were observed in 26 of the 31 cases that could be regarded as selected at random. Grossly visible foci of hemorrhage were present in 46 of the total series of cases and in 19 of the cases in the random series. Infiltrations of leukemic cells in the brain were described in 42 cases, and in 36 of these cases there was hemorrhage in or surrounding the foci of infiltration. Hemorrhage of a proportion to be the immediate cause of death was present in the brain in 27 of all the cases and in 9 of the 31 cases in the random series.

The foci of leukemic cells occurring in the brain in cases of leukemia are similar in all respects to those seen in other somatic tissues in this disease and represent foci of proliferating leukemic cells in the tissue. The infiltrations of leukemic cells in the brain are thought to be an important factor in the production of the hemorrhages in the brain associated with leukemia, since hemorrhage without an accompanying infiltration with leukemic cells was infrequent. Both hemorrhage and infiltrations of leukemic cells in the brain showed a greater predilection for the white than for the gray matter. There does not appear to be any significant difference in the production of lesions in the brain and the development of neurologic signs and symptoms among the various types of leukemia, although hemorrhage and leukemic cell infiltration were slightly more frequent in the chronic than in the acute forms of leukemia.

Neurologic signs and symptoms attributable to the leukemic disease were present in 34 of all the cases included for study but appeared in only 11 of the 31 cases in

the random series. Neurologic symptoms were the first clinical manifestation of the leukemic disease in 5 of the cases. Hemiplegia was observed in 11 cases and was always accompanied with a hemorrhage in the brain of a proportion to be the immediate cause of death. In rare instances neurologic signs and symptoms were exhibited without demonstrable pathologic change in the brain. Signs and symptoms of increased intracranial pressure sufficient to indicate a space-occupying intracranial lesion were only rarely observed, in spite of the fact that in many instances the infiltrations of leukemic cells involved large parts of the brain.

WINKELMAN, Philadelphia.

CORTICAL CEREBELLAR ATROPHY WITHOUT ATAXIA: II. PRIMARY CIRCUMSCRIBED VARIETY. BEN W. LICHTENSTEIN and SAMUEL A. LEVINSON, *J. Neuropath. & Exper. Neurol.* 5:29 (Jan.) 1946.

Lichtenstein and Levinson report 3 cases of atrophy of the cerebellar cortex. The first patient, a Negro, aged 37, was struck on the head with a baseball bat. He became unconscious immediately and was admitted to the hospital within an hour. There was no previous history of disability. The patient was comatose and restless. The scalp was lacerated. Blood was seen in the right external auditory canal, and the mandible appeared deformed. Spinal puncture revealed uniformly bloody cerebrospinal fluid. The patient remained in coma and died twelve days after the accident. Necropsy revealed multiple, sharply circumscribed areas of panatrophy of the cerebellar cortex, characterized by absence of all parenchymatous elements, persistence of the Golgi-Bergmann layer of glia cells and intense gliosis of the degenerated areas. The pons and medulla oblongata were not examined.

The second patient, a Negro woman aged 52, had had pain and weakness in both lower extremities for about six months. For a few weeks she had noted numbness of the legs and weakness of both upper extremities. The only pertinent findings on neurologic examination were tenderness of the lower extremities to pressure, bilateral overactivity of the patellar and Achilles reflexes and a positive Babinski sign on the right. Position sense and two point discrimination were lost below the knees.

Study of the blood revealed a hemoglobin concentration of 71 per cent, with 4,800,000 red blood cells. The Kahn reactions of the blood and cerebrospinal fluid were negative. Lumbar puncture revealed normal manometric readings. The cerebrospinal fluid protein measured 90 mg. per hundred cubic centimeters. The patient's clinical course was downhill, despite parenteral injections of liver. The neurologic signs progressed, and the patient had pronounced weakness of both upper extremities, with greatly exaggerated tendon reflexes and a bilateral Hoffmann sign. All sensation was lost below the knees, and urinary and fecal incontinence ensued. Pathologic study revealed multiple, sharply circumscribed areas of atrophy of the cerebellar cortex affecting all the varieties of the parenchymatous elements (parenchymatous panatrophy of the cerebellar cortex, incomplete type) and scattered foci of changes in the nerve cells of the nuclei pontis and the inferior olfactory bodies, with atrophy of many of the nerve cells and disappearance of others.

The third patient, a white female infant with an Arnold-Chiari deformity, died at the age of 6 months of hydrocephalus complicating a lumbosacral meningocele. Study of the brain revealed multiple areas of incomplete panatrophy of the cerebellar cortex, characterized by absence of the cells in the external granular layer and of the Purkinje cells and by great diminution of the cells in the granular cell layer.

The study indicates that parenchymatous degeneration of the cerebellar cortex may be a primary disorder, or it may be secondary to degeneration elsewhere in the nervous system. The degeneration may affect only one type of cell exclusively or predominantly, or it may affect all types of parenchymatous elements. Parenchymatous degeneration of the cerebellar cortex is to be looked on as a histopathologic state and not as a disease entity, for it may be observed in a variety of disorders. Sharply circumscribed areas of primary atrophy of the cerebellar cortex characterized by degeneration of the parenchymatous elements and secondary gliosis probably represent the end state of a degenerative process. The pathogenesis is unknown, and many factors, particularly pressure, may play an important role in its causation. The disorder may be asymptomatic and be discovered accidentally at necropsy.

GUTTMAN, Philadelphia.

OLIVOPONTOCEREBELLAR ATROPHY IN A CAT. JOHN W. SCHUT, *J. Neuropath. & Exper. Neurol.* **5:77** (Jan.) 1946.

An adult cat, killed in an acute experiment, was observed on removal of its brain to possess an abnormally small cerebellum.

The olivopontocerebellar atrophy in this case resembled in incomplete form a similar disorder observed in man. Except for absence of changes in the external arcuate nuclei, the resemblance extended even to such specific characteristics of the human disease as the relative preservation of the vermis and flocculus of the cerebellum, the preservation of the central cerebellar nuclei and the variable involvement of the Purkinje cells. The presence of microscopic changes, such as decrease in the number of Purkinje cells and reduction in the number of nerve cells in the pontile nuclei, permits a differentiation of this case from cerebellar aplasia, hypoplasia or agenesis. True atrophy of the cerebellum in a cat has heretofore not been described.

GUTTMAN, Philadelphia.

SPINAL TRACTS SUBSERVING MICTURITION IN A CASE OF ERB'S SPINAL PARALYSIS. J. McMICHAEL, *Brain* **68:162**, 1945.

McMichael reports clinical and autopsy studies on a woman aged 47 with urinary retention and weakly extensor plantar responses. Examination of the spinal fluid revealed a slight increase of total protein and a positive Wassermann reaction. Antisyphilitic therapy did not alter the clinical picture. The patient died of bilateral infected hydronephrosis and necrotizing cystitis. The pia-arachnoid over the dorsal aspects of the cord was thickened and milky white, and histologic examination revealed perivascular lymphocytic cuffings. Sections of the spinal cord stained for myelin sheaths demonstrated a bilaterally symmetric zone of degeneration anterior to the posterior horns and superficially placed in the lateral columns. McMichael indicates that sensory afferent and motor efferent fibers subserving micturition may pass in the posterior and superficial parts of the lateral columns.

FORSTER, Philadelphia.

Meninges and Blood Vessels

TULAREMIC MENINGITIS: REVIEW OF THE LITERATURE AND REPORT OF A CASE WITH POSTMORTEM OBSERVATIONS. BYRON M. STUART and ROSCOE L. PULLEN, *Arch. Int. Med.* **76:163** (Sept.) 1945.

Stuart and Pullen report the case of a Negro aged 34 who was admitted to the hospital because of confusion and inability to recognize familiar people and

objects. Five days prior to admission, the patient had a severe shaking chill with profuse sweating. Several hours later, he had a severe headache, which became mild the following day. About thirteen hours prior to admission to the hospital, he felt "dumpy," soon became confused and disoriented and failed to recognize familiar people and objects.

On physical examination the patient was uncooperative, agitated, confused and disoriented and had to be restrained. The temperature was slightly elevated. The pulse rate was 58 per minute and the respiratory rate 20. The pertinent laboratory finding was mild leukocytosis, with a shift to the left. Serologic tests for syphilis gave negative reactions. Lumbar puncture on the day of admission yielded spinal fluid under a pressure of 34 cm. of water. The fluid was turbid and contained 960 white cells per cubic millimeter, with 60 per cent large lymphocytes and 40 per cent small lymphocytes. There was a 4 plus reaction for globulin. The sugar measured 45.4 mg. and the chlorides 643 mg., per hundred cubic centimeters, and the colloidal gold curve was 00012340220. A smear of the spinal fluid showed no organisms. Culture of the spinal fluid yielded no growth in twenty hours. Two days after admission the patient began to spit up frothy and bright red blood. The respiration and pulse were poor; some degree of rigidity of the neck was noted, and examination of the chest still revealed nothing abnormal. On the third day after admission the patient had two generalized seizures. He was treated with sulfapyridine, administered intravenously. He died six days after admission to the hospital.

Gross examination of the brain at necropsy revealed clear spinal fluid. The subarachnoid vessels were greatly dilated. There were a few patches of grayish white exudate in both hemispheres, particularly in the frontal regions. These were limited to the sulci. Microscopic examination of the brain revealed a few small and large round mononuclear cells, of inflammatory character, in most sections of the meninges. All sections of the cortex showed extreme congestion and severe degeneration of ganglion cells, the latter being greatly out of proportion to the degree of inflammation. Disappearance of ganglion cells was also noted in the basal ganglia and in the brain stem. There was an abundance of yellow, pigmented granules, some of which were free and some within the large mononuclear cells. The infiltration was severest in the choroid plexus. The ependyma of the lateral ventricles showed plaque formation and subependymal gliosis. In the medulla there were several subependymal petechiae.

Culture of the lungs revealed streptococci. Guinea pigs inoculated with substance from the lungs and the brain became ill and were studied at autopsy on the fourth day. Each showed numerous miliary lesions in the spleen consistent with the diagnosis of tularemia.

The authors state that tularemia should be considered in the diagnosis of obscure forms of meningitis and, in turn, evidence of meningeal involvement should be sought for in gravely ill patients with tularemia. To date, no patient with tularemic meningitis has recovered. There are now, in all, 6 reported cases in the literature. It is stated that therapy is of no avail, although one should use all available chemotherapeutic agents, including penicillin, the sulfonamide compounds and Foshay's antiserum.

GUTTMAN, Philadelphia.

NEUROLOGIC COMPLICATIONS DURING MENINGOCOCCIC MENINGITIS TREATED WITH SULFONAMIDE DRUGS. THOMAS W. FARMER, Arch. Int. Med. 76:201 (Oct.) 1945.

The purpose of this paper is to outline the clinical course and prognosis in a variety of neurologic complications of meningococcic meningitis. The data were

obtained from a study of approximately 300 patients with meningococcic meningitis during the years 1942, 1943 and 1944. About 100 of the patients were children. Of the 300 patients, focal neurologic complications were observed to develop in 26 during the course of meningococcic infections. In each of these patients it was ascertained that the paralysis did not exist before the onset of the meningeal infection, and that no other neurologic disease was concomitant with the meningitis.

The etiologic diagnosis was established for 24 of the 26 patients by the isolation of meningococci, group I, from the cerebrospinal fluid. For the remaining 2 patients, presumptive diagnoses were based on the observations of meningeal signs, a petechial cutaneous eruption and purulent cerebrospinal fluid. All 26 patients received sulfonamide therapy: Sixteen received sulfadiazine; 7 were treated with sulfamerazine; 2 received sulfapyrazine, and 1 was treated with sulfathiazole. All the patients recovered.

The 26 patients with focal neurologic abnormalities were carefully followed for three years. Among them were 9 patients with paralysis of the sixth nerve, 9 with paralysis of the seventh nerve, 5 with paralysis of the eighth nerve and 3 with transient focal cerebral complications.

Paralyses of the cranial nerves present characteristic clinical features. Paralysis of the sixth nerve, the most common palsy of the extraocular nerves, usually develops early in the course of meningitis, when the cerebrospinal fluid is purulent. It is usually unilateral, and complete recovery within a few weeks is the rule. Unilateral and bilateral paralyses of the seventh nerve are usually late complications, which develop after the cerebrospinal fluid has become clear. In 4 patients with facial diplegia late onset of paralysis during convalescence was characteristic. Recovery of function usually requires several months. It is complete in most, but not in all, cases. Paralysis of the eighth nerve with deafness is the most serious complication of the cranial nerves. It occurs more commonly among children than among adults and is usually bilateral. Its present incidence is approximately 5 per cent. It may develop during the acute meningitic infection, during convalescence or even after recovery. Deafness is permanent in the vast majority of cases. In young children deaf-mutism results. Occasional cases of transitory deafness also occur.

Cerebral complications with convulsions and transient hemiplegia occur rarely. They usually appear late in the course of the infection, with clear cerebrospinal fluid. The convulsions may be unilateral or generalized. They are followed by hemiparesis with occasional aphasic disorders and hemianopsia. Electroencephalograms reveal focal disturbances in the area involved. All these neurologic and electroencephalographic signs were observed to clear completely, with no residual signs.

GUTTMAN, Philadelphia.

ADRENAL HEMORRHAGES IN MENINGOCOCCIC SEPSIS. J. SCHWARZ, Arch. Path. 41:503 (May) 1946.

A fulminant type of sepsis, with purpura and cyanosis of the skin and adrenal hemorrhages, frequently occurring in the presence of a thymolymphatic constitution, especially in children, and generally caused by *Neisseria meningitidis* (*Neisseria intracellularis*), is wrongly given the name "Waterhouse-Friderichsen syndrome." Neither Waterhouse nor Friderichsen, but Voelcker, in 1894, was the first to describe this syndrome. Waterhouse, in 1911, and Friderichsen, in 1918, published studies, the merit of which does not justify the use of the name "Waterhouse-Friderichsen syndrome," suggested by Thomas and later by Glanzmann and others.

A descriptive term, such as "fulminant sepsis with adrenal hemorrhage" or "meningococcic adrenal syndrome" is more appropriate and less erroneous than the present name.

The intracranial anatomic lesions have been described as varying from "none" to the presence of purulent meningitis or encephalitis, but in several cases in which macroscopically there were no lesions meningitis was demonstrated microscopically; therefore, in cases in which clinically there are no meningeal signs and in which macroscopic inspection of the leptomeninx does not appear to show anything abnormal there may be definitive inflammation of this membrane.

In the cases observed, inflammatory lesions were not seen in the adrenal glands, nor was thrombosis of the adrenal veins observed. Definite hyperplasia of the thymus and hypoplasia of the adrenal glands occurred.

WINKELMAN, Philadelphia.

TREATMENT OF CHRONIC INFLUENZAL MENINGITIS: HEPARIN AS ADJUVANT.

E. S. PLATOU, R. W. GIBBS and F. H. ADAMS, *Journal-Lancet* **66**:157 (May) 1946.

Platou and his associates show that heparin given intrathecally in the acute stages of infantile meningitis is worthy of trial to avert chronicity, with its potentially serious or fatal sequelae. In chronic meningitis due to *Hemophilus influenza* the problems of exudate in the small avenues of communication of the foramen and the subdural spaces, lack of adequate concentration of antibody in these areas and insufficiency of bacteriostasis may arise singly or in combination. Poor drainage, disparity in the character of fluid from the ventricle and the spinal canal, abnormally high protein levels and persistently low sugar levels are suggestive adjuncts to diagnosis in the presence of clinical signs of rigidity, tremor, opisthotonos and growth of the organism in cultures of the cerebrospinal fluid. Intrathecal serum may furnish the desired concentration but may also enhance the problem because of local antibody-antigen reaction. Heparin may help liquefy exudate, and air injected later may open the delicate pathways so that curative mediums may reach their goal. Recent studies suggest that streptomycin may complement, or even supplant, sulfonamide compounds as a bacteriostatic agent against *H. influenzae*. The 3 cases reported meet the criteria of chronic influenzal meningitis. Intrathecal and intraventricular therapy was carried out with antibody. Heparin, air and injection of complement, as well as specific therapy, as suggested by Alexander, were used. The treatment was successful.

J. A. M. A.

TREATMENT OF PNEUMOCOCCIC AND STAPHYLOCOCCIC MENINGITIS WITH PENICILLIN AND SULFONAMIDES: REPORT OF 20 CASES. W. H. HALL, J. ALDEN, G. M. BURT and W. W. SPINK, *Minnesota Med.* **29**:553 (June) 1946.

Of 17 patients with pneumococcic meningitis whom Hall and his associates treated with penicillin, 13 recovered. Sixteen of the 17 patients received sulfadiazine or sulfamerazine in addition to the penicillin. Of 3 infants with staphylococcic meningitis who were treated with a combination of penicillin and sulfonamide drugs, 2 recovered. The authors recommend that in the treatment of suppurative meningitis due to pneumococci or staphylococci penicillin be administered intravenously or intramuscularly and intrathecally. In addition, sulfadiazine or sulfamerazine should be given orally or parenterally, but not intrathecally. The importance of early diagnosis, supportive treatment and eradication of suppurative foci is stressed.

J. A. M. A.

Diseases of the Brain

ASPHYXIA OF NEWBORN INFANTS. J. D. RUSS and R. A. STRONG, *Am. J. Obst. & Gynec.* **51**:643 (May) 1946.

Russ and Strong studied 1,048 cases of asphyxia in newborn babies. Mild asphyxia occurred in 471 cases, with 3 deaths; moderate asphyxia occurred in 420 cases, with 14 deaths, and severe asphyxia occurred in 157 cases, with 52 deaths. Anoxemia, from many causes, is responsible for 18.5 per cent of all deaths in newborn babies. Among the most frequent contributing factors of anoxemia are the age and parity of the mother, duration of labor, type of delivery, prepartal analgesia and the anesthetics used during delivery. Less frequently, prematurity, premature separation of the placenta, bleeding placenta previa or short cord may cause anoxemia. Anoxemia prolonged more than two minutes after delivery will cause serious cerebral changes. Prompt initiation and maintenance of respiration within thirty seconds after cutting the cord will prevent these changes, and if respiration is established before two minutes it may oxygenate the blood sufficiently to arrest any changes which have begun. Actual aspiration with the use of an intratracheal catheter and subsequent insufflation of the lungs constitute the truly reviving technic. The after-care of the newborn resuscitated baby is of equal importance with the resuscitation itself.

J. A. M. A.

PLEURAL SHOCK AND CEREBRAL EMBOLISM. J. B. ANDOSCA and J. A. FOLEY, *Am. Rev. Tuberc.* **52**:221 (Sept.) 1945.

According to Andosca and Foley, pleural puncture, employed in pneumothorax therapy, in aspiration of an empyema cavity or in exploratory thoracocentesis, may result in signs and symptoms which have been diagnosed as pleural shock or as cerebral embolism. The confusion which exists between the two diagnoses gives a false impression concerning the seriousness of the complication. Pleural shock is rare and may occur in excitable and neurotic patients, but the symptom complex of cyanosis, changes in respiration and circulation, convulsions, ocular disturbances, loss of consciousness, aphasia, paralysis and sometimes death occurring during pleural puncture is definitely due to cerebral embolism. The treatment consists in lowering the patient's head and giving cardiac stimulants. The prognosis in a case of cerebral embolism depends on the amount of air entering the blood stream and the region of the brain most seriously involved. The authors have encountered 12 cases, with 3 fatalities, in a series of 90,120 pleural punctures at the Boston Sanatorium. One of the fatal cases was attributed to procaine hydrochloride poisoning. Procaine hydrochloride in a 1 per cent solution should be employed only for the initial pneumothorax treatment, and not for the subsequent refills.

J. A. M. A.

CRANIOTOMY AND TOTAL DISSECTION AS METHOD IN TREATMENT OF ABSCESS OF THE BRAIN. E. F. FINCHER, *Ann. Surg.* **123**:789 (May) 1946.

According to Fincher, results as seen in the literature on cerebral abscess which have been removed in toto have been surgically ideal. These wounds have healed by primary intention, and the patients have escaped the prolonged complications of hospitalization, and often fatal results, that have followed other methods of treatment. In the author's 5 cases radical total dissection was carried out, aided by sulfonamide and penicillin therapy; and the period of hospitalization has been comparable to that of a normal convalescence period for any craniotomy. The

morbidity, with 1 exception, has been nil. The results thus far have been such as to suggest that the basic surgical principle of "incision and drainage" in the treatment of abscesses of the brain might be replaced by total dissection of the abscess and primary closure of the wound.

J. A. M. A.

CHANGES IN THE CENTRAL NERVOUS SYSTEM ASSOCIATED WITH ENCEPHALITIS COMPLICATING PNEUMONIA: I. A CLINICAL STUDY. A. B. BAKER and H. H. NORAN, *Arch. Int. Med.* **76**:146 (Sept.) 1945.

Baker and Noran report the histories of 6 patients who had some form of encephalitis associated with pneumonia. Two of the patients were infants; 1 was a 10 year old girl, and the remaining 3 were adults. The authors believe that, in view of the type of cerebral complications which take place, the organism which is responsible for the pneumonia probably does not produce the encephalitis. They therefore limit the etiologic field to three considerations: (1) the toxic theory, (2) the virus theory and (3) the allergic theory.

The observations presented indicate that, regardless of the causative organism, complications of the central nervous system may follow pneumonia. The severity of the encephalitis does not correlate with the severity of the pulmonary involvement. In other words, relatively mild pneumonia may be followed by severe cerebral damage.

Clinical pictures produced by involvement of the central nervous system can be divided into five types, each showing definite clinical characteristics which may be of both diagnostic and prognostic significance: (1) the type characterized by generalized symptoms of a nonspecific nature (headache, vomiting, lethargy and irritability), (2) the delirious type, (3) the convulsive type, (4) the lethargic type and (5) the hemiplegic type.

GUTTMAN, Philadelphia.

CAUSE, EFFECT AND TREATMENT OF AIR BLAST INJURIES. R. E. TUNBRIDGE, *War Med.* **7**:3 (Jan.) 1945.

Injuries due to air blast are best divided into three types: mild, moderate and severe.

The mild injuries are readily overlooked. The symptoms are not severe—tightness of the chest, pain under the sternum or in the chest, irritable and paroxysmal cough or slight deafness; in fact, they may appear to be so out of keeping with the general well-being of the patient as to lead to their being considered psychosomatic manifestations. Treatment consists of rest, mild sedation and reassurance. Recovery is complete within fourteen days.

The moderate injuries are frequently accompanied with other injuries, and the visual evidence of wounds often leads to the overlooking of injuries due to air blast. Associated surgical conditions should be treated on their merits, and operation or blood transfusion should not be withheld on account of the presence of blast injuries. The prognosis of severe wounds associated with blast injury is worse than that of wounds not so complicated, but treatment, namely, rest and administration of oxygen, is not affected.

The severe injuries present no problem because the patient rapidly loses consciousness and usually dies within twelve hours. Temporary relief is sometimes afforded by venesection, but morphine is the chief therapeutic weapon.

The sequelae from air blast are few: deafness and postconcussive syndromes. The pulmonary lesions in persons with nonfatal injury, unless secondarily infected, resolve completely.

PEARSON, Philadelphia.

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DISSOCIATED PARALYSIS OF THIRD NERVE DUE TO A MENINGIOMA EN PLAQUE OF THE LESSER WING OF THE SPHENOID BONE, REVEALED BY ROUTINE ROENTGENOGRAPHIC EXAMINATION OF THE SKULL. R. GARCIN, M. KIPFER, M. ROSIER and H. X. MAN, *Rev. neurol.* **77**:153 (May-June) 1945.

A man aged 20 was seen on March 25, 1944 because of paralysis of the right third nerve of six months' duration. All the external muscles of the right eye supplied by the third nerve were involved and there was mild ptosis. There was no internal ophthalmoplegia. This dissociation of involvement of the internal and the external musculature of the eye at first suggested a central lesion, perhaps a virus infection. There was no syphilis or diabetes. Routine roentgenograms of the skull showed abnormal density of the lesser wing of the right sphenoid bone and narrowing of the right sphenoidal fissure. Mild headache in the right frontal area appeared in November 1944. An operation was performed on December 13. A meningioma *en plaque* was observed in the region of the lesser wing of the right sphenoid bone. The dissociated nerve paralysis persisted after the operation.

N. SAVITSKY, New York.

PEARLY TUMOR OF THE CEREBELLOPONTILE ANGLE. T. ALAJOUANINE and R. THUREL, *Rev. neurol.* **77**:196 (July-Aug.) 1945.

Alajouanine and Thurel report an unusual case of pearly tumor of the cerebellopontile angle, with successful operation. The sudden onset with peripheral facial palsy was unusual, the palsy being the only symptom for ten years. The patient, a man aged 44, had sudden onset of palsy of the left side of the face, of peripheral type, at the age of 30; this persisted for fourteen years, with no sign of improvement. Ten years after the onset, tinnitus and loss of hearing appeared on the left side. Deafness was complete in the left ear three years afterward. Attacks of dizziness began to recur eleven years after the onset; two years later difficulty with equilibrium became worse. Almost fourteen years after the onset, the clinical findings were complete palsy of the left side of the face, peripheral in type; mild involvement of the left trigeminal nerve; abolition of the left corneal reflex, and fibrillations in the left masseter muscle. There were complete deafness on the left side with absence of caloric responses, spontaneous horizontal nystagmus toward the right, outward past pointing on the left, a tendency to veer backward and to the right in the Romberg position and signs of cerebellar involvement on the left. The fundi were normal. Operation revealed a rather large pearly tumor in the left cerebellopontile angle. There was no trace of the left facial nerve, and the left eighth nerve appeared very thin. The patient's condition improved after the operation, despite transitory dysphagia, and he was able to return to work. The dizziness and nystagmus disappeared; the deafness improved somewhat. The paralysis of the face remained unchanged.

N. SAVITSKY, New York.

Peripheral and Cranial Nerves

ACUTE INFECTIOUS POLYNEURITIS (GUILLAIN-BARRÉ TYPE). JOSEPH G. CHUSID and GILBERT H. MARQUARDT, *Ann. Int. Med.* **23**:852 (Nov.) 1945.

Chusid and Marquardt report the case histories of 6 patients who became ill with acute infectious polyneuritis while they were in India. At one time or another all these patients had symptoms which included paresthesias, dysesthesias and various types of paresis. Neurologic signs included palsies, pareses and sensory disturbances of the cranial nerves. Four of the patients had gastrointestinal symptoms and diarrhea during some stage of their illness. In several of the cases the

first diagnosis was acute anterior poliomyelitis. The authors state that the differentiation between so-called acute infectious polyneuritis of the Guillain-Barré-Strohl type and acute anterior poliomyelitis can be made chiefly on the finding of albumino-cytologic dissociation of the cerebrospinal fluid with the former.

GUTTMAN, Philadelphia.

FACIAL PARALYSIS IN ACUTE OTITIS MEDIA AND USE OF PENICILLIN. EDWARD M. GLASSBURN, Arch. Otolaryng. 41:218 (March) 1945.

Facial paralysis occurring during the course of acute otitis media is a rare and alarming development. It occurs approximately once in every 200 cases. Possible causes advanced for the paralysis are: (1) infection of the nerve by contact, (2) compression of the nerve by hyperemic blood vessels which accompany the nerve, (3) lymphangitis in the facial nerve canal and (4) toxic paresis of the vasomotor nerves and consequent disturbances in the nutrition of the nerve.

In the last few years, the literature on the occurrence of facial paralysis early in the course of acute otitis media stresses conservative, nonoperative treatment. Prior to the advent of the sulfonamide drugs, mastoidectomy was advocated on an emergency basis, regardless of the time of onset of the paralysis. Introduction of the sulfonamide drugs, together with the more recent advent of penicillin, has led to a critical analysis and revision of surgical indications in cases of acute otitis media and mastoid disease. That the appearance of facial paralysis in cases of this type will be regarded as a medical, and not a surgical, problem is strongly suggested by the efficacy of penicillin in the treatment of acute otitis media.

Glassburn reports 3 cases of facial palsy which occurred during the course of acute otitis media. Under a conservative medical regimen, the progress was satisfactory. Two patients received penicillin in addition to sulfonamide therapy, while 1 received only sulfadiazine. The return of function for hearing and facial motion was complete in all cases. The author believes that the recovery from facial paralysis is dependent on immediate control of the otitis and that the trend toward conservative treatment of otitic facial palsies will be advanced by the results of penicillin therapy.

RYAN, Philadelphia.

VERTIGO IN HYPOTHYROIDISM. A. G. ATHENS, Minnesota Med. 29:562 (June) 1946.

Athens reviews observations on 30 patients who had recurring attacks of vertigo, fatigue, a low basal metabolism and low blood pressure. Desiccated thyroid generally gave relief from symptoms in the 25 patients who were treated. There is a similarity between this symptom complex and Ménière's syndrome. The author suggests the possibility of attacks of vertigo being precipitated by the accumulation of waste metabolic products in the endolymph and advises that routine basal metabolic studies and determinations of the blood cholesterol be made in patients with Ménière's symptom complex.

J. A. M. A.

COCHLEAR DEAFNESS. A. J. WRIGHT, Proc. Roy. Soc. Med. 39:265 (March) 1946.

Many otologists consider that Ménière's disease is an entity and that the auditory disturbances, in the form of deafness and/or tinnitus, precedes the vertigo in the majority of cases, often by a long period. The present paper endeavors to draw a more detailed picture of the disease as seen in the absence of vertigo.

Most commonly occurring in an adult, of either sex, the disease is occasionally observed in children. The earliest symptom is usually tinnitus, with a variable period elapsing before any appreciable deafness is observed. Occasionally (in 7 per cent of cases) a dramatically sudden onset is reported. Trauma is frequently given as the exciting cause, including everything from an explosion to a cold draft of air. Again, paracusis may be the original symptom, or hyperacusis, the latter being frequently accompanied with tinnitus. The amount of hearing loss varies; subjectively it is usually reported as unilateral, although careful measurements reveal bilateral involvement. In 8 per cent of the author's cases there was high grade deafness in both ears, and the deafness was usually definitely bilateral at the onset. The type of hearing loss is perceptive, although care must be taken in interpretation, as often a mistaken diagnosis of conduction deafness is made with the tuning fork tests. The earliest loss is usually for high tones; later all tones are involved. There is, however, no typical audiogram for Ménière's disease. Masking of the good ear in the Rinne test is essential, especially in cases of pronounced unilateral deafness. Weber's test does not so frequently lead to error.

A frequent, and often early, symptom is paracusis, which may persist to a late stage. It is described as a general distortion and jangling of sounds, but a musical ear may perceive notes as sharp or flat; in 6 cases in the author's series the high tones were sharp, the low tones flat. The presence of variability in hearing is almost diagnostic, and tinnitus often follows the same course. Sensory phenomena, ranging from a sense of fulness to actual pain and headache, are noted in the majority of cases. The complaint of unpleasantness, or even pain, associated with loud noises may be found in the early or late stage of the disease. Often the earliest symptom, and the most constant, is tinnitus, which was found to be absent in only 4 per cent of the author's cases.

In 20 per cent of the author's cases there were old changes in the tympanic membrane or the middle ear, consisting of scarring, opacity or retraction. On several occasions, in addition to gross disease, a dilated vessel down the handle of the malleolus or, rarely, a hyperemic blush on the inner tympanic wall was seen.

BERRY, Philadelphia.

VESTIBULAR INJURIES. T. CAWTHORNE, Proc. Roy. Soc. Med. **39**:270 (March) 1946.

In a study based on the comparison of 120 cases of deliberate destructive operations on the labyrinth for the relief of Ménière's disease and 58 cases of closed head injury with labyrinthine signs, Cawthorne concludes that in cases of persistent vertigo following concussion the vestibular end organ is the likely seat of damage. The clinical picture is complicated by psychologic disturbances, often sufficient to divert attention from the underlying cause, but explanation of the true nature of the state of affairs and a series of graduated exercises encouraging movements of the head and eyes form the most satisfactory basis for hastening recovery. If this regimen of treatment is begun soon after operation, return to useful occupation is expected within a month, and chronic invalidism need not result from head injuries.

Although pathologic proof is lacking, postconcussion vertigo is assumed to be due to damage of the end organ in the labyrinth because of similar clinical signs and symptoms in the two conditions. In nearly all the observed cases of prolonged vertigo the condition was the result of "acceleration concussion," in which the head was freely movable at the time of injury. The author explains by analogy: In the cochlea exposure to loud sounds may result in a disturbance of the endolymph sufficient to cause permanent damage to the organ of Corti. Both cochlear and vestibular end organs rely for essential stimulus on displacement or deformation by movement of the endolymph, and it is reasonable to suppose that if one end organ suffers actual damage from overstimulation, the other may suffer in a like manner. "The facts that vertigo is the cardinal symptom in a damaged labyrinth, and that a frequent sequel of concussion is vertigo support this hypothesis."

The author describes clinically what he terms the syndrome of "acute vestibular failure": overwhelming vertigo, "awful sickness" and turbulent movements of the eyes, all increased on movement of the head. This syndrome is seen when a previously functioning labyrinth is completely and suddenly overwhelmed, whether by operative procedures of labyrinthotomy or labyrinthectomy or by head injury. The intensity varies from case to case and may be masked by the effect of injuries elsewhere. The acute phase subsides within a few days, leaving a residual vertigo consisting of a sensation of apparent movement, either objective or subjective, typically induced by sudden alteration in posture or turning of the head. Other residual symptoms include a sensation of slight movement of the ground, like the roll of a ship; inability to focus the gaze on an object for any length of time and the dislike of looking at rapidly moving objects; instability in the dark and on climbing and descending stairs or an inclined plane, and a tendency to tire quickly on physical exertion. Headache, though common in cases of concussion, is infrequently observed after labyrinthine operations and is discarded as part of the vestibular disorder.

Of the 58 cases of head injury, deviation from the normal in response to caloric stimulation was present in 56, and in 1 of the remaining cases vertigo had disappeared several days prior to the caloric test. Of the 56 cases, damage to the cochlea was present in only 24.

In discussing Cawthorne's thesis, Mr. E. D. D. Davis commented on 57 cases of injury to the ear resulting from fractured skull in his experience; in only 5 of these was there demonstrated damage to the internal ear, which in all but 1 case was limited to the cochlea. Labyrinthine damage was found in 1 case. He postulates cerebral concussion or damage as the cause of vertigo following head injuries.

BERRY, Philadelphia.

PARALYSIS OF THE RADIAL NERVE DUE TO SERUM THERAPY (PATHOGENIC ROLE OF URTICARIA). T. ALAJOUANINE, R. THUREL and R. TRICOT, *Rev. neurol.* **77**:130 (May-June) 1945.

A man aged 44 sustained an injury to the left index finger on Nov. 22, 1944. Two days later 10 cc. of tetanus antiserum was injected into the right thigh. On November 30 serum sickness with generalized urticaria appeared; this cleared up in forty-eight hours. On December 2 he began to complain of pain in the neck and the upper limbs. After sleeping flat on his back for two or three hours, he awoke with a left wrist drop. The pain had become less severe and was localized to the paralyzed limb. All muscles supplied by the radial nerve except the triceps were involved. There was some diminution of sensation in the dorsal aspect of the first interosseous space. The completeness of involvement with sensory and motor components of the nerve favored the explanation that urticarial swelling exerted a mechanical effect on the nerve fibers. The authors emphasize that involvement of periscapular muscles is not pathognomonic of serum paralysis.

N. SAVITSKY, New York.

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Book Reviews

Are You Considering Psychoanalysis? By Felix Ocko, M.D. Edited by Karen Horney, M.D. Price, \$3. New York: W. W. Norton & Company, Inc., 1946.

This book is written for popular use. There has been a great increase in interest on the part of the laity in psychology, psychiatry and psychoanalysis. To many people psychiatry and psychoanalysis are synonymous, so that persons who have had one or two meetings with a psychiatrist of any school of thought believe that they are being "analyzed," and that every psychiatrist is automatically a psychoanalyst. For such persons this book will be truly informative.

Most educated Americans have heard of Freud and read some of his writings with more or less understanding. One of the well known writers on analytic subjects in America has been Dr. Karen Horney, whose books have had a wide circulation. Originally a member of the orthodox Freudian school of psychoanalysis, Dr. Horney has enlarged on and revised certain of Freud's formulations to the extent that she has become the founder of a new school of psychoanalysis, utilizing the basic contributions of Freud. When the Association for the Advancement of Psychoanalysis was founded in 1941, the program on community education in psychoanalysis included a series of lectures for the laity, given by recognized analysts, all of whom are affiliated with the association. This book is the outgrowth of one of the series of lectures. As editor, Dr. Horney has given the book unity. The authors include Drs. Horney, A. R. Martin, Valer Barbu, Muriel Ivimey, Harold Kelman and Elizabeth Kilpatrick. As in all books associated with Dr. Horney, the fluidity and lucidity of the presentation are especially commendable.

An attempt is made to answer and expound the many questions asked by the person considering psychoanalysis. "What is a neurosis?" "Why psychoanalysis?" "What Do You Do in Analysis?" "What Does the Analyst Do?" "How Does Analysis Help?" and "How Do You Progress After Analysis?" are the titles of some of the chapters. The basic concepts of all schools of psychoanalysis are explained in nontechnical language, together with the differences and emphases of the several derivative groups. This is given in a cursory manner. Emphasis is placed on the Horney viewpoint that psychoanalysis is equally concerned with "what goes on between individuals" and "disturbances inside the individual." The focus is "on the individual in his human environment or social setting in its broad sense."

The psychoanalytic credo of the Horney school is stated so succinctly as to bear quotation: "We believe that man is constructive by nature and becomes destructive only when his genuine urge to grow and develop has been frustrated. It is upon these latent constructive forces in the patient and his environment that we count so heavily to help him out of his difficulties. We believe that man by his own efforts can free himself of the consequences of those inimical forces which made him destructive. We believe that within the limitations of his natural endowment and those imposed and created by his parents, his culture and his physical environment, man can exercise a choice regarding the ways and directions of his self-betterment. We believe that people can live together in a truly democratic society and in a spirit of mutuality even though for the present, and for some time to come, the strongest stimuli driving them toward that goal may be a survival need and a fear of the consequences of the monstrous destructiveness created and unloosed."

Psychoanalysis is a growing experience for the patient. During analysis the patient will "visualize goals and work toward their attainment. These goals are—becoming acquainted with yourself as you are (not as you think you are); understanding your particular conscious and unconscious attempts at solutions of problems which confront you; evaluating these solutions and their effects on your life;

changing conditions in your personality by resolving neurotic conflicts, and when your real self has become free, mobilizing your resources in directions of your own choosing."

The profound change in personality structure of the patient which is the goal of the analysis should indicate to the prospective patient that analysis is more than just a confession or a mother-child teaching relationship, in which specified rules for untroubled living are dispensed. The patient must work out the various bases for his neurotic trends, working through the resistances his unconscious presents. The technic of this is briefly explained. The patient may feel humiliated, angry, frightened and anxious as he begins to learn more truths about himself and is faced with the need of doing something about them. The relationship with the analyst is an intense one, never a passive experience. The analysis may be a tremendous task for the patient. But it is a cooperative enterprise. The analyst endeavors to find out together with the patient in what manner he is blocking his own way. His main task is to help the patient live "under his own jurisdiction," recognize his own wishes and find his own set of values. Through his interpretations, explanations and questions, the analyst influences the course of the analysis, the final goal being a whole and well integrated personality.

A final chapter of unusual interest is called "How Do You Progress After Analysis?" It emphasizes that analysis is not a definitive procedure in the sense that all patients who have completed an analysis emerge from the process as completely integrated, secure individuals who will never have any further problems. Analysis is not an absolute attainment. As Dr. Horney states: "It is an endless road toward a destination it never reaches." But it does make the analysant aware of his true goals, and guides and prevents him from aimlessly stumbling through life by giving him inner strength and freedom.

The more practical aspects to a patient considering analysis—Who should my analyst be? How long will it take? How much will it cost?—are discussed briefly in an early chapter.

While the book is definitely directed toward the person who is already considering analysis as a means to help himself, or is at least aware of his need for psychiatric help, and as such performs an essential function in an admirable manner, it is to be regretted that nowhere within its covers is there any discussion of the applicability of psychoanalysis or of some of its basic tenets to the better functioning society as a whole.

A Textbook of Clinical Neurology. By J. M. Nielsen. Second edition. Price, \$7.50. Pp. 699, with 190 illustrations. New York: Paul B. Hoeber, Inc., 1946.

The personal flavor given to a textbook is usually to be found in the preface and in the last few words before the index. This is abundantly true in the new edition of this excellent volume. Nielsen himself is little short of a walking encyclopedia of neurology, and has probably gone farther than anybody else living in familiarizing himself with the landmarks in clinical neurology. These he lists with the observation, "They have been gathered here as fundamental works with which all students should be acquainted."

Yet Nielsen's work is not in any sense encyclopedic. It is far from a recitation of dull facts that have been handed down from textbook to textbook together with the accumulation of the barnacles of error that are so often perpetuated. Every page bears the imprint of his own thinking and experience, and these have been both wide and profound. The case reports and illustrations are fresh and are taken from that museum of living pathology which is the Los Angeles County Hospital, supplemented by specimens studied at the Cajal Laboratory of Neuro-pathology, directed by Courville.

Nielsen is at his best in the field of clinical cerebral localization, and his chapters on aphasia, apraxia and agnosia are masterly in their practical delineation of this particularly difficult field. He has revised the sections on electro-encephalography, sulfonamide compounds and penicillin in order to present the current understanding of these diagnostic and therapeutic methods. His "organic"

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orientation causes him to take a sly dig or two at "certain faiths which teach that all disease is due to erroneous thoughts," and he wisely limits the discussion of disorders of the vegetative nervous system to the physiologic aspects rather than include the whole subject of psychosomatic medicine. The student, he believes, can gain the necessary orientation in this field from recent psychiatric texts. Nevertheless, the section on the psychoneuroses serves to round out the presentation of clinical neurology as given in the rest of the volume.

Nielsen's book is a large one, crammed with facts, but, fortunately, these facts are presented in such a way that the students will be able to harmonize them and thereby gain a much better grasp of the whole field of clinical neurology.

Their Mothers' Sons: The Psychiatrist Examines an American Problem.

By Edward A. Strecker, M.D. Price, \$2.75. Pp. 220. Philadelphia: J. B. Lippincott Co., 1946.

This book is a warning to mothers of the United States to liberate their sons and thus make for less neurosis in American society. The reader will find in this volume an excellent description of the different forms and expressions of "mother love" and the subtle means that "Mom" uses to keep her son from becoming a mature man. Strecker stresses the responsibility of the sincere mother slowly, intelligently and kindly to wean her son from herself and so develop in him the independent strength of maturity. The volume is recommended.

The Anatomy of the Nervous System: Its Development and Function. By Stephen Walter Ranson, M.D., Ph.D., Late Professor of Neurology and Director of Neurological Institute, Northwestern University Medical School, Chicago. Revised by Sam Lillard Clark, M.D., Ph.D., Professor of Anatomy, the Vanderbilt University School of Medicine, Nashville, Tenn. Eighth edition. Price \$5. Pp. 532, with 417 illustrations, 14 in color. Philadelphia: W. B. Saunders Company, 1947.

The new generation of medical students will be happily introduced to their neuroanatomy, not through the dark green-covered "Ranson," so familiar to and prized by their predecessors since 1920, but to the new, brown-covered Ranson-Clark edition, which will likewise long merit the approbation of their successors. Thus have the publishers marked the designation of Dr. Clark by Dr. Ranson himself as his successor.

The co-author has well fulfilled Dr. Ranson's hopes. The eighth edition emerges as an up to the minute, basic book, for cognizance has been taken of all facts gleaned from recent studies on man, monkeys, cats, rabbits, dogs and chicks. The addition of some fifty new worldwide contributions to the bibliography of five hundred odd references attests the thoroughness of the revision. Thus the researches have amplified and clarified some aspects of knowledge of the cerebral cortex, cerebellum, choroid plexus and trigeminal pathways; the cochlear, vestibular and optic nerves, and the thalamic nuclei, and these sections have been rewritten.

The presentation of material has been altered for easier use by consolidating all gross descriptive anatomy into one opening section. Most of the original, incomparable, illustrations have been retained, and an excellent new series of nine parasagittal sections of the human brain stem has been added.

The book is highly recommended as achieving its purpose of presenting the developmental and functional significance of structure of the nervous system and its correlation with the interpretation of normal and pathologic physiology. The earnest student cannot fail to get excellent orientation as a neuroanatomist and neurologist.

Über nichthypophysäre Chiasmasyndrome. By M. Gil Espinosa. Pp. 60. Basel, Switzerland: S. Karger, Ltd., 1946.

This little monograph is a review of the various conditions, exclusive of primary tumor of the pituitary gland, capable of producing a chiasmal syndrome. It con-

tains nothing new and covers rather sketchily a large and complicated subject. No new material is contained within it except that the author adds to the usual suprasellar causes of the chiasmal syndrome cholesteatoma, granuloma, chordoma, angioma, chondroma and parasitic infections. The bibliography is inadequate.

Technic of Psychoanalytic Therapy. By Sandor Lorand, M.D. Price, \$2.50. Pp. 251. New York: International Universities Press, Inc., 1946.

This book is the outgrowth of Dr. Lorand's course in technic which he gives regularly at the New York Psychoanalytic Institute.

Outstanding in this book is the absence of any rigid rules. The author consistently stresses flexibility—flexibility implemented by a thorough personal analysis, as well as accumulative experience. However, this flexibility must take place within the framework of the freudian conception of psychodynamics.

Paramount emphasis is laid on the transference situation and its correct analysis. Thus, in chapters headed "Anxieties and Phobias," "Sexual Difficulties in the Male," "Sexual Difficulties in the Female," "Compulsion Neuroses" and "Neurotic Depressions," the author points out the patterns that transference takes in those clinical categories. The analyst must be ever sensitive to the transference situation and its correct analysis.

The author's chapter on countertransference reflects his great experience in psychoanalytic technic. As a training analyst, he has had the opportunity to observe the innumerable pitfalls of the young analyst, and in this chapter he records the stumbling-blocks which are encountered.

This book answers many questions, but leaves a good number unanswered. However, the psychoanalysts apparently do not intend to spoon-feed students. Too many broad statements are made which require better elaboration. Analysts, in building up a thesis, have a disconcerting manner of stating, "Of course, this means . . ." or "it is obvious that. . . ." The author is no exception. Unfortunately, those deductions are not so obvious as the author implies. It may be obvious to him and to other trained analysts, but certainly not to the student.

To those who have a good groundwork in freudian psychoanalysis, this book is highly recommended.

Physiologie oculaire clinique. By A. Magitot. Paper. Price, 750 francs. Pp. 458, with 230 illustrations. Paris: Masson & Cie, 1946.

Magitot has been interested in ocular physiology for the last forty years. His book on the iris (L'iris, Paris, Gaston Doin & Cie, 1921) is a classic, and he has published innumerable papers on various phases of ocular physiology, more particularly on the circulation of the eye and the regulation of ocular tension. He retired from active duty in the Lariboisière Hospital, of Paris, in 1940 and thus has been enabled to collect his papers and write this excellent book.

It is noticeable that it was written by an ophthalmologist, not a physiologist, for the author has constantly in mind the need of explaining clinical features.

There are fifteen chapters, some of which will be of interest only to ophthalmologists, but others are closely related to the field of neurology. Physiologic optics has purposely been left aside. Chapter 1 deals with the physiology of the lids and of lacrimation. Chapter 2 is devoted to the trigeminal nerve and the autonomic nerves and centers. In the next three chapters the author discusses at length the problems of ocular tension and nutrition, and in chapters 6 and 7, the physiology of the cornea and the conjunctiva. The next chapter, on the iris and pupil, is, of course, of particular interest to the neurologist. Chapters 9, 10 and 11 (on the lens and retina) are, again, more strictly ophthalmologic, but the last four chapters are those to which neurologists will mostly turn (chapter 12, the optic nerve and visual fields; chapter 13, the visual cortical area; chapter 14, oculomotor physiology, and chapter 15, binocular vision).

The numerous illustrations are excellent, there is a good index, and references are given at the end of each chapter.

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The Peripheral Circulation in Health and Disease. Robert L. Richards, M.D. Price, \$6. Pp. 153. Baltimore: Williams & Wilkins Company, 1946.

This book is an investigation into one aspect of the function of the autonomic nervous system—a study of peripheral circulation, mainly by the method of measurement of skin temperature. As such, there are two basic chapters on spontaneous and imposed variations in vasomotor activity, to which future workers using the skin temperature method will undoubtedly refer. They contain, in addition to a critical review of pertinent literature, a reevaluation of the influence of environmental temperature, basal metabolic rate, food, exercise, sleep and changes in posture on the temperature of the limb. They emphasize the concept of vasomotor gradient and describe the use of the limb immersion method as a relatively simple method of producing reflex vasodilatation and vasoconstriction. Diagnostic nerve block, reactive hyperemia and artificial pyrexia are also evaluated.

The clinical section of the book is disappointing if one expects full study of all aspects of peripheral circulatory disease; but, restricted though the book may be, important methods of study using skin temperatures are well presented and the value of such study in prognosis and treatment is indicated. Occlusive vascular disease and Raynaud's phenomenon are each considered as a whole. A chapter on vasomotor changes following complete and incomplete division of the peripheral nerve presents the clinical picture (warm and cold phases) and discusses interestingly the theoretic implications of the two phases. This chapter is based on a study of 350 patients with lesions of the main nerve trunks to the limbs and is a complete essay in itself, worth the reading. There is a final chapter on the immersion foot syndrome.

In all, this book is a careful clinical contribution to one phase of the study of the autonomic nervous system.

Clinical Examination of the Nervous System. By G. H. Monrad-Krohn. Eighth edition. Price, \$4. Pp. 380, with 126 illustrations. London: H. K. Lewis & Co., Inc., 1947.

The middle-aged teacher of neurology has watched this exceptionally useful primer grow in the past twenty-five years from hip pocket to brief case size. It has lost none of its flavor, although with the excellent new illustrations some thought might be given to revising the truly ancient ones that have been inherited from the past. In his preface the author expresses his enthusiasm for neurology: "Whilst some twenty or thirty years back even in many civilized countries neurology was regarded only as a by-product of internal medicine or of psychiatry, it is today everywhere recognized as an independent branch of medicine of central importance. Everywhere the number of neurological and neurosurgical clinics is steadily increasing."

Considering that Norway was almost completely cut off from the outside world during the war, Monrad-Krohn has performed an excellent task in keeping up with the neurologic literature. This work makes no pretense to covering the field of clinical neurology; it is, rather, a clinical manual that the student may carry with him to the bedside for the exploration of a patient with disease of the nervous system. In this edition more emphasis is placed on ancillary investigations than has been done in past editions. Sections on roentgenography, encephalography and angiography, accompanied with excellent illustrations, enhance the value of the work and show what the well equipped neurologist should be able to obtain in the way of information from his patient. Myelography, however, is only briefly mentioned. The author adheres to his purpose in concentrating on localization and leaves the question of diagnosis of the nature of the lesion to the student of the larger books. When the student has definitely localized the disease process, the evolution and nature of the disease may become evident. The book can be read with pleasure as well as with profit, for the language is unaffected and clear.